Long-term Exposure to Ambient Air Pollution and Trajectories of Cognitive Decline in Northern Manhattan

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ABSTRACT

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Age-related cognitive decline is a growing public health issue as increases in life expectancy are expected to substantially raise the prevalence of cognitive impairment and dementia. An estimated 46.8 million individuals are currently living with dementia, with the global prevalence expected to double every 20 years. Emerging evidence suggests that ambient air pollution from traffic and other sources may be an important risk factor for cognitive decline in addition to its association with other cardiovascular and neurological outcomes.

The aim of this dissertation was to first investigate the association between long-term exposure to ambient air pollution and cognitive decline among older adults in an urban population within Northern Manhattan. I then set out to assess specific mechanisms involved in the association between long-term exposure to ambient air pollution and cognitive decline, specifically investigating the ApoE4 allele, age, and current smoking behavior as effect modifiers of the association between long-term exposure to ambient air pollution and cognitive decline.

I found evidence of an adverse effect of ambient air pollution on the cognitive functioning of older adults. Overall, exposure to higher levels of ambient air pollution was highly predictive of

lower cognitive scores, but at baseline only. Contrary to the current hypothesis, limited evidence was found for an association between estimates of air pollution and trajectories of cognitive decline. The patterns of effect were similar across pollutant types and cognitive domains in this aging, urban population. I found strong evidence of effect modification by smoking status, where contrary to the hypothesis; the overall effects of ambient air pollution on cognition and cognitive decline were stronger among individuals who never smoked. The impact of effect modification by age category was most prominent in the memory and language cognitive domains. Among individuals less than 75 years old at baseline, there was a stronger association between a one IQR increase in air pollutants and cognitive domain scores at baseline as compared to individuals 75 years and older. I did not observe conclusive evidence of an association between air pollution and cognition in models stratified by APOE-ε4 status.

To my knowledge, this is the largest study to analyze the association of ambient air pollution on cognition and cognitive decline over time in a racially and ethnically diverse sample. These results further support the current evidence on the role of air pollution on accelerated cognitive aging and brain health.

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CHAPTER ONE.

Effect of Long-term Exposure to Ambient Air Pollution and Cognition in Older Adults: A review

INTRODUCTION

As the global population continues to age, age-related cognitive decline is an increasingly important public health issue. An estimated 46.8 million individuals are currently living with dementia, with the global prevalence expected to double every 20 years (1). In addition, healthcare expenditures for cognitive impairment reached 818 billion dollars in 2015 and are expected to reach a staggering two trillion dollars by 2030 (1).

The expected increase in morbidity and mortality due to cognitive decline has important public health implications and identification of risk factors is of vital importance. Non-modifiable risk factors for cognitive decline have been consistently identified in the literature, with age being the strongest known risk factor (2–4). Research has suggested there may be a genetic component, as a family history of dementia as well as the presence of the Apolipoprotein E genotype E4 (APOE-ε4) allele are strong predictors of the disease (2,4).

While evidence behind non-modifiable risk factors is strong, there is no consensus around key modifiable risk factors for cognitive decline (2,4). Independent researchers, however, have identified a rather sizeable list of potential risk factors. Cerebrovascular disease, particularly stroke, has been shown to double the risk of dementia (5–9), while subclinical cerebrovascular disease not only increases the risk of incident dementia, but also accelerates progression of the disease and causes more significant decline in cognitive function (10–14). In addition, growing evidence suggests that brain health is very closely linked to the health of the cardiovascular system, thus sharing many of the same lifestyle and psychosocial risk factors (3,15). Smoking (16–19), diabetes (20–24), obesity and being overweight (21,25), high cholesterol (26,27), and hypertension (HTN) (20,28,29) are all associated with risk of accelerated cognitive decline. Physical activity and moderate alcohol use have protective effects; heavy drinkers, on the other hand, have a more than three-fold increased risk of dementia (30–35). In addition, cognitive reserve, defined as having higher educational attainment, IQ, or occupational attainment may protect against the onset of cognitive decline (36–44), while depression throughout the lifespan increases the risk of cognitive decline (45–47). In almost all studies, it was suggested that control of risk factors is more important in midlife, lending evidence to the idea that physiological mechanisms that start the progression of cognitive decline may begin much earlier in life.

Disagreement about the influence of traditional risk factors has led to a search for novel risk factors for cognitive decline. There is growing interest in the adverse health effects of environmental toxins; among the most pervasive is ambient air pollution. Air pollution is a largely ubiquitous environmental exposure and is quickly becoming a widespread public health hazard, particularly in urban areas. It is estimated that long-term exposure to ambient particulate matter caused 7.6% of total global mortality in 2015, making it the fifth-ranking global mortality risk factor (48). Despite significant decreases in overall levels of ambient air pollution over the last decade, levels still remain high. As of 2011, 124 million people in the United States were living in areas that did not meet the United States Environmental Protection Agency (EPA) National Ambient Air Quality Standards (49). Studies have long reported on neurotoxic effects of environmental exposures on the central nervous system and brain (50–52), but the relationship between exposure to air pollution and cognition in older adults has received less consideration than non-environmental risk factors (53,54). Older adults are particularly sensitive to their physical surroundings and studies have suggested they are especially vulnerable to the health effects of adverse environmental environments (55–57). The ability to reduce air pollutants on a population level makes it a very interesting modifiable risk factor, as the public health impact of any intervention could be substantial.

Ambient air pollution, a mixture of over 40 toxic substances, is comprised primarily of solid and gaseous pollutants, combustion products, and organic compounds (49,58–61). Often considered the most widespread threat is particulate matter (PM), a heterogeneous mixture of particles that is a result of fuel combustion, transportation, and industry (58,62). Nitrogen Oxide (NO_x), generated from the combustion of fossil fuels, increases exponentially with traffic density on major roadways and in urban areas. It is rapidly oxidized to Nitrogen Dioxide (NO_2), and both are often measured when assessing traffic emissions (58). It is difficult, if not impossible, to truly differentiate individual pollutant effects in large epidemiologic studies due to constant chemical reactions that occur between pollutants (58). The major pollutants described above are present together but distributions in the pollutant mixture may vary by location, source of toxin, weather patterns, or season of the year.

Recently implicated as a modifiable risk factor for cognitive decline, the concern over adverse health effects of air pollution is not new. The relationship between air pollution and respiratory disease is one of the most robustly documented relationships of environmental factors and health.

Early studies focused on 'trigger' effects of pollution, where short-term exposure to high levels of pollutants increased the risk of respiratory-related events and emergency department visits and hospitalizations for both children and adults (63–78). Evidence of a trigger effect has also been demonstrated for increased hospitalizations for cardiovascular disease (CVD) (79,80), myocardial infarction (MI) (81), and ischemic stroke (82–94).

The evidence supporting the deleterious health effects of long-term exposure to ambient air pollution is growing, though results are not unanimous. Overall, long-term exposure to pollution has been shown to be associated with increased risk of morbidity and mortality due to CVD (63,67,95–106) , but several studies have reported contrasting results (79,102,107) .The pattern between long-term exposure and neurological disorders is similar. Increased exposure to air pollution has generally been associated with an increased risk of cerebrovascular events (95,101,108–112), however several studies have reported null associations (80,113). Prior research has also shown that living in highly polluted areas is associated with higher rates of overall mortality (97,114–122). In addition, the effects of air pollution have been shown to be associated with several cardiovascular risk factors including diabetes (123–125), total cholesterol and triglycerides (126), blood pressure (126–129), and C-reactive protein (130). The relationship between long-term exposure to traffic pollution and subclinical cerebrovascular disease, a well-documented risk factor for cognitive decline, has been examined in only a few studies with inconsistent results (131–135). The relationship between subclinical disease, particularly subclinical brain infarctions and white matter hyperintensities, and air pollution may be important for the mechanistic progression of cognitive decline, as it indicates that the influence of air pollution may be affecting brain health long before any clinical symptoms manifest.

While the evidence linking air pollution with the cardiovascular and cerebrovascular systems suggest it may also have a damaging impact on the brain and cognitive processes, research on the effects of pollution on the nervous system is limited (136–138). A key limitation of studying cognitive decline and dementia in epidemiological studies is that these are clinically diagnosed disorders based upon patterns of onset and trajectories of decline (3,139). There is substantial biological overlap; many patients with dementia pathologies also have a history of cerebrovascular disease making it difficult to distinguish between dementia and other comorbid neurological conditions. Definitive etiology is often not determined before death and subsequent autopsy. There is a high degree of variability in studies which examine cognitive decline and dementia, likely due to limitations in defining the disease as well as measures used to evaluate cognitive functioning (140–143). Epidemiological studies often use a series of tests to evaluate various domains of cognition including attention, learning, memory, language, visuospatial skills, and executive functions, though most studies do not comprehensively measure all functional domains due to time and cost restraints (4). Therefore, I conducted a structured review and critique of the existing epidemiologic studies analyzing an association of ambient air pollution with an outcome of cognition, cognitive decline, or dementia-related diagnosis.

METHODS

Utilizing the assistance of an experienced, professional academic reference librarian, I performed a structured literature search focused on first identifying all relevant human studies related to ambient air pollution and cognition. Materials included peer-reviewed journal articles identified through searches of PubMed and EMBASE electronic databases for peer-reviewed, published papers and a search of ProQuest Dissertations, a database of global dissertations and theses. Electronic databases were searched using a combination of MESH/EMLINE terms (based on database searched) and keywords. Relevant literature was identified using any/all combinations of an exposure and an outcome term (Table 1.1).

Only articles assessing the long-term effects of air pollution, defined as measuring exposure over time periods greater or equal to 6 months prior to measurement of outcome were included in this review. This search was further limited to human studies, and all articles were restricted based on MeSH and EMLINE terms to include studies tagged ("humans") and ('human'/de), respectively. Papers were further excluded if they were not written in English, as were case studies, reviews, and conference abstracts or scientific reports, or those articles that did not examine some component of the association between long-term ambient air pollution and cognition.

RESULTS

The literature search applied to all articles included in all databases through November 30, 2017. A total of 754 unique articles written in English were identified using this detailed search strategy (Figure 1.1). After title and abstract review and removal of duplicates, 40 unique papers were sent to full text review (114,144–181). Twenty-seven articles were deemed relevant and remained for inclusion into this structured review (114,144,148,150,151,154,155,160,164–181). The bibliographies of these 27 papers were examined for additional relevant articles, but this did not add any novel articles. Included papers and relevant study characteristics are summarized in Table 1.2.

I begin first with a discussion of the published evidence linking pollution exposure and age-related cognitive decline in a narrative review. I then address some of the limitations of current studies and areas for potential bias. The collected literature was examined by type of ambient air pollution, study design and population, and variations in exposure and outcome assessment.

Ambient Air Pollution and Cognitive Decline in Older Adults

While research generally supports the hypothesis that long-term exposure to air pollution is positively associated with poorer cognition and accelerated cognitive decline, the association was not universal and there does not appear to be a sufficiently clear pattern of association across studies.

The most frequently studied component of traffic pollution studied was PM. Cross-sectional associations between exposure to $PM_{2.5}$ and various measures of cognitive function were found in 4 relatively large cohorts of community-dwelling older men and women, the Health and Retirement Study (HRS) (174), American's Changing Lives (ACL) longitudinal study (148,154), the National Social Health and Aging Project (NSHAP) (151), and the Heinz Nixdorf Recall Study (172) . A study of 1,496 adults living in the greater Los Angeles area found no association between air pollution and a global cognitive score, however $PM_{2.5}$ was associated with lower verbal learning scores, NO_2 was inversely associated with logical memory, and ozone (O_3) was associated with lower executive function and higher logical memory (178) . A fifth cross-sectional study found $PM_{2.5}$ to be associated with hospital admissions for dementia and AD in 9.9 million Medicare enrollees from 50 urban areas in the northeastern United States (170) . There was a 15% increase in risk of admission for individuals exposed to higher levels of $PM_{2.5}$.

Longitudinal analyses done in the Ontario Population Health and Environment Cohort (OPNHEC), a population-based cohort study of all Ontario adults, found an IQR increase in both $PM_{2.5}$ and NO_2 to be associated with increased risk of incident dementia (HR_{adj}: 1.06 and HR_{adj}: 1.10, respectively) (155). In the same cohort, living closer to a major roadway was also associated with an increased incidence of dementia(144). Within this cohort there was no association between O_3 and incident dementia (155).

While the relationship between $PM_{2.5}$ and cognition is relatively consistent, several studies did not find significant associations. A cross-sectional analysis of 20,150 adults in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort found no increase in odds of cognitive impairment with increased exposure to $PM_{2.5}$ (181). Few meaningful relationships between $PM_{2.5}$ and cognition were found in the Study on the Influence of Air Pollution on Lung Function, Inflammation, and Aging (SALIA) cohort (164) or the Nurses' Health Study (NHS) (173).

Several studies indicated that $PM_{2.5}$ may be more deleterious to health than PM_{10}. The Whitehall II longitudinal cohort study found that while both $PM_{2.5}$ and PM_{10} were associated with cognitive decline over 2 time points, stronger effect sizes for the association of $PM_{2.5}$ were seen.

Similarly, PM_{10} was analyzed longitudinally over several time points among men and women enrolled in the Cardiovascular Health Study (CHS) (132). While associations for PM_{10} and diagnosis of Alzheimer's Disease or dementia were null, there was a significant association between exposure to PM_{10} and cognitive performance; a 10 $\mu g/m^3$ increase in PM_{10} was associated with -2.6 lower Mini-Mental State Exam (MMSE) score and -1.1 point lower digit symbol substitution test (DSST) score. Two cross-sectional studies among women aged 68-79 years living at least 20 years at the same residence in the SALIA study found no significant association between PM_{10} and Consortium to Establish a Registry for Alzheimer's Disease (CERAD)-plus scores (164,179). Similarly, studies of NHANES examinees (180) and women within the NHS (173) saw null results between PM_{10} and cognition.

While the analysis of the Heinz Nixdorf Recall Study found significant associations between $PM_{2.5}$ and diagnosis of mild cognitive impairment (MCI), the study found no significant associations between PM_{10}, $PM_{10-2.5}$, NO_x, and NO_2 and cognitive function (172). This was one of only five studies which actually utilized a clinical diagnosis of cognitive decline or dementia. A longitudinal study looked at the effect of NO_2 and carbon monoxide (CO) on a clinical diagnosis of dementia ascertained from health insurance records of 29,547 Taiwanese individuals aged >50 (169). The overall risk of incident dementia increased as exposure to CO and NO_2 increased, but the results were only significant when comparing highest versus lowest quartiles of exposure. Using the same source of administrative data, a second study captured the effect of PM_{10}, O_3, and $PM_{2.5}$ at baseline on first diagnosis of Alzheimer disease among 95,690 individuals 65 and older (168). An increase in both O_3 and $PM_{2.5}$ levels from baseline to diagnosis of AD were significantly associated with risk of AD diagnosis. The longitudinal analysis of NO_x and clinical diagnosis of dementia assessed every 5 years among 1,806 individuals from the Betula Study in Northern Sweden found that risk of dementia was significant when comparing highest versus lowest quartile of exposure (171). In contrast, a longitudinal analysis of PM_{10} and NO_2 modeled as monthly estimates over several time points and clinical diagnosis of AD and dementia diagnosis in the CHS found no significant associations (132).

Two studies using the Chinese Longitudinal Health and Longevity study found significant associations between an Air Pollution Index (API) and decreased cognitive function as measured by MMSE scores. The first cross-sectional study looked at 7,358 elderly residents of urban China and found a highly significant association between MMSE and API in fully adjusted models, with a 1-point increase in API associated with a 0.51-point decrease in MMSE Score (165). The second study of 15,593 individuals used longitudinally obtained cognitive data from the 3rd and 4th waves to ascertain cognitive impairment over time, defined by having MMSE <18. Results showed that a 1-point increase in API increased the odds of developing cognitive impairment by 9% (114).

Two cohorts have provided evidence on the effect of Black Carbon (BC) on cognition. Several analyses done in the Veterans Affair Normative Aging Study (NAS) found that in a cohort of white men, doubling of the estimated BC exposure was associated with a significantly higher risk of lower MMSE score and lower global cognitive function in a cross-sectional analysis (150,160,166,177). A longitudinal analysis with 17 years of follow-up on 765 participants in the

MOBILIZE Boston Study found that BC was associated with having a MMSE score less than 26 (175). BC was not associated with any of the other 5 neuropsychological tests performed (verbal learning, verbal memory and executive function, attention and psychomotor speed, working memory, executive function), however smaller distance to roadway was associated with poorer performance on verbal learning, attention and psychomotor, letter and category fluency tests.

Limitations of Existing Studies

Study Design and Characteristics

The primary limitation of the current literature is the inability to distinguish between association and causality. Of the 27 studies, over half were cross-sectional, making it impossible to determine causality as it cannot be determined whether exposure to pollution occurred before or after negative cognitive effects were present. The 11 remaining studies were longitudinal, designed to examine long-term exposure to air pollution and its influence on cognitive function. Of those studies, half ascertained both exposure and outcome over time, while the other half used a baseline measure of air pollution, allowing only outcome to vary over time. It remains unclear if either longitudinal study designs are better in regards to getting a clear picture of the causal pathway between air pollution and cognition. It is well documented that cognitive decline begins to manifest physiologically before there are clinical symptoms and pollutant levels earlier in life may be more influential (1). It is probable that these studies aren't measuring the exposure at a time in which it has substantive impact on cognitive processes. Some of the longitudinal studies may also be limited by a short duration of follow up, with follow-up times ranging from 4-17 years. These studies may not have followed patients long enough for them to develop cognitive decline, introducing a selection bias. This right censoring of cases, if dependent on exposure, may cause measures of effect to bias towards the null. There is also evidence of differential results due to study design, highlighting the importance of this limitation. The Whitehall II study, for example, found that in a cross-sectional analysis four measures of air pollution were associated with lower reasoning and memory scores, however only $PM_{2.5}$ and PM_{10} were associated with steeper cognitive decline in longitudinal analyses over two time points (176).

A second important limitation to the current research is that all 27 studies had inclusion criteria requiring that participants have complete cognitive and air pollution data. Despite studies reporting substantial amounts of missing data on both cognitive function and exposure few tested the ramifications of the missing data using sensitivity analyses (174,175,178–180). Individuals with poor cognitive function at baseline are likely not captured by these studies as they are less likely to come in for study visits or undergo neuropsychological testing. There may be a selection bias towards those with intact cognitive function or those who are healthier overall, biasing results towards the null. Studies using large, population-based cohorts or health insurance registries may be less impacted by this bias, however, as there is little reason to expect their involvement in the registry would be associated with their exposure or cognitive status (144,155).

In addition, measures of air pollution are often only available in urban areas where monitoring stations are available. Some studies have begun to assess the increased risk of cognitive decline among those living in urban areas independent of any other factors (148,182–184), however results show it is unlikely that cognitive decline is impacted by urbanicity alone. Instead, a a combination of factors such as socioeconomic status and education may make individuals more likely to live in urban areas and also contribute to accelerated cognitive decline.

In addition to a loss of generalizability due to missing data, the use of specific sub-populations may also contribute to biased results. Age is a very important risk factor for cognitive decline and dementia, therefore the age of the population being studied may substantially influence effect estimates. In older populations, the number of adults with cognitive decline is expected to be higher, regardless of exposure status, therefore any absolute rates ascertained from older populations may be higher. The study with the youngest subjects looked at a sample of NHANES examinees aged 20-59 (180). Ten of the studies had mean ages ranging from 60-65(144,148,154,155,169,172,174,176,178,181) while the remaining 16 studies had a mean age greater than 70 years old (114,132,150,151,160,164–166,168,170,171,173,175,177,179). In general, the studies with a mean age greater than 70 years old had stronger effect sizes than those with a younger mean age. In addition, characteristics such as sex and race-ethnicity may influence results. The prevalence of cognitive decline and dementia is higher in women (185,186) and non-Hispanic whites (187–193), while older African Americans are twice as likely and Hispanics are 1.5 times as likely as older non-Hispanic whites to develop incident dementia (187–193). Several studies used single-sex populations, so it is feasible to suggest that effect estimates in women-only studies may be higher but also that there is inherently more selection bias into the study due to higher rates of cognitive decline at study enrollment. In the current studies it is almost impossible to distinguish between these issues and similar issues around race-ethnicity, as there is no available information for individuals not included in the study.

Exposure Assessment

Another key challenge in interpreting findings of existing studies is the inconsistent way in which both air pollution and cognitive decline are defined. Much of the available evidence was derived from cohorts originally designed to investigate other exposure-disease relationships, thus limited by methodological issues in the assessment of both exposure and outcome. In most studies, exposure data was gathered prior to or at the time of cognitive testing, however duration, type, classification, and level of pollutant varied widely.

First and foremost, studies used several different methods of defining and measuring exposure. While all measures (PM, NO_x, NO_2, CO, BC) are common sources of ambient air pollution, they exist together in a complex mixture. It is very difficult to measure a single marker of air pollution as they are highly correlated with each other. Studies tend to analyze one or several components, but often do not look at the full picture of how overall the mixture influences health. Several studies have looked at a series of components using consistent definitions of cognitive decline and found discordant results across pollutants. For example, researchers using the SALIA cohort looked at the effects of $PM_{10,}$ NO_2, NO_x, $PM_{2.5}$ on the effects of CERAD-plus score and found that only NO_x was associated poorer cognitive function (164). In addition to utilizing different components of air pollution, the characterization of these components is not universal. Statistical results may differ depending on how the exposure is analyzed, whether as a continuous or categorical variable, and further, how the groups are categorized. It will be important in future studies to utilize many measures of pollution in the same study, to see if there exists one with more power than others, and also to identify if different mixtures of these pollutants are important. More broad measures of air pollution have been analyzed; a series of studies in China used an air pollution index (API) (114,165), and others have calculated distance to nearest roadway as an indirect measure of traffic pollution (144,175,179). While these measures may better measure the mixture of harmful air pollutants, they do not allow analyses to be adjusted for traffic concentration, speed of vehicles, and land use characteristics such as green space that may influence actual exposure levels.

There is also concern of measurement error when trying to measure and define individual exposure level based on residential estimates. Most estimates of traffic pollution are indirect, based on spatiotemporal modeling from monitors across the study area, a method that has been shown in validation studies to lead to biased results due to misclassification of exposure (194,195). In addition, many of the geographical locations at which the pollution was measured are imprecise. Approximately half (n=16) measured estimates at the residential location while the remainder measured at larger geographical areas such as census tract, block group, postal code, or city. While residential estimates do not account for data on time spent in other locations outside the home, larger definitions may suffer ecological bias which assumes that each person is being exposed to the same levels of pollutants. Few studies ascertained time living at residential address, further adding to the misclassification of true long-term exposure levels. Those that did adjust for length of time at residence in their models saw similar patterns of results as in the unadjusted models(148,150,160,174,177), however in the study of PM_{10} and $PM_{2.5}$ and cognitive decline in the NHS, sensitivity analyses were restricted to women who didn't move between 1988 and first cognitive assessment in 1995, revealing modestly stronger measures of effect

(173). Measurement error in these studies would likely be non-differential, leading to slightly attenuated results which could be causing a higher proportion of null and non-significant results. While the most sensitive way to measure exposure to air pollution would be to utilize personal air monitoring devices, they are expensive and may not be practical for measurement of long-term exposure in large, longitudinal epidemiological studies. Attempts to mitigate bias due to these methodological difficulties in defining and estimating long-term measures of air pollution could be done by categorizing pollution in multiple ways, measuring different components, and utilizing several durations of time in defining long-term exposure within the same study with the same cognitive outcomes. At this time, it is difficult to make comparisons between differences in air pollution exposures when cognitive measures are also different, and vise-versa. Therefore, a study which analyzes several versions of one while holding the other constant would identify relationships that could be then tested in other populations.

Assessment of Cognitive Function

Similarly, the definition and measurement of cognitive decline is not consistent across studies. First and foremost, most studies measure only cognition function at a single time point in a cross-sectional study. Even among longitudinal studies, few actually measured a decline over time. In addition, there is not a standardized definition for cognitive function or decline; instruments used to measure cognition vary and may be measuring different components of cognition. In 27 studies, over 30 different tests were used to measure cognitive function. The majority of studies used a combination of cognitive screening tests or a more sensitive neuropsychological test battery. Studies varied in whether they used the test results to create a study-specific global cognition score to assess global abilities, or grouped into domains which test language, memory, executive function, and visual processing. This is an important consideration as different pathologies of dementia manifests differently across domains, for example poor performance on memory tests is often indicative of AD while deficiencies in executive function are characteristic of vascular dementia. Studies testing only certain domains may not capture all pathologies of cognitive decline. Further, even when studies used the same measure, they were often categorized differently for analysis. For example, the Mini-Mental State Exam (MMSE) was used in several studies and analyzed continuously on a scale of 1-30, or categorically with >26 considered cognitively intact, or in another <18 considered as cognitively deficient. In addition, independent tests of cognitive function may be too simple to ascertain cognitive decline; while there may be a statistical difference in outcomes based on a single continuous measure it may not be of clinical significance. Only seven studies defined their outcome as incident or prevalent dementia using clinical standards or hospitalization records (132,144,155,168–172).

Identification of a Causal Pathway

Cognition represents a complex combination of domains which include attention, learning, memory, language, visuospatial skills, and executive function. The reasons behind cognitive decline are multi-causal and therefore it is likely that air pollution is only a small component of the causal pie which leads to accelerated cognitive decline and dementia. Therefore, it is very important to measure and account for potential confounders, mediators, and modifiers in any analysis in order to ascertain the true relationship between air pollution and cognitive function.

Adjustment was carried out in all studies for a wide variety of potential confounding factors. Most studies included demographic characteristics (e.g. age, sex, race-ethnicity), sociodemographic characteristics (e.g. individual SES or income, educational attainment, employment status), and cardiovascular risk factors (e.g. smoking habits, alcohol use, physical activity, hypertension, myocardial infarction, stroke, depression status, diabetes, weight). Several studies also included census-tract or community level confounders such as proportion of residents without high school degree, median household income, and urbanicity to attempt to adjust for any confounding by community (114,144,148,154,155,174–176). Overall, addition of confounders into subsequent models attenuated, be it modestly, the effects of the crude association between measures of air pollution and cognitive decline. However, most studies still had the potential for bias due to residual confounding. Most cohorts weren't designed to measure psychological outcomes and therefore may not measure all important confounders. Other factors such as indoor air pollutants and dietary habits were not generally assessed, which could have substantial associations with cognition (196,197). It is also very difficult to completely remove confounding due to socioeconomic status (SES) because it is a complex construct not easily encompassed by variables such as education and income.

It is feasible that many of these cardiovascular processes may mediate, instead of confound, the process by which air pollution causes cognitive decline. As discussed, many cardiovascular risk factors are associated with an increased risk of cognitive decline. In addition, exposure to air pollution has been linked to an increased risk of these factors. It seems appropriate, therefore, to consider cardiovascular risk factors not as confounders but instead as mediators along the potential causal pathway between air pollution and cognitive decline. Only 5 studies treated cardiovascular and respiratory risk factors as potential mediators instead of confounders, and did so by including a series of factors such as BMI, HTN, MI, and lung disease in the same model (173,174). Other studies individually looked at carotid media intima thickness (178), urbanicity (181), and stroke (132) as potential mediators. All five studies which assessed mediation as a potential causal pathway, however, reported no change in effect size after doing so (171,173,174,178,181). While this may give a preliminary look at potential mediating pathways, it doesn't allow for the identification of a single mediator and a vascular pathway of mechanisms cannot be determined. In addition, there were no studies which included inflammatory markers as mediating factors, despite evidence that pollution may be associated with inflammation and that inflammation contributes to risk of cognitive decline and dementia (198–202).

There is also limited evidence on the existence of effect modification by either behavioral or clinical cardiovascular risk factors. While age is considered a significant risk factor for cognitive decline, it was only analyzed as a potential effect modifier in one study (179). Ranft et al. found that living 5-m from a high traffic road was associated with lower CERAD-plus scores in women <74 years old, but in those > 74 there was no association. Tzivian et al. found that depression was also a significant effect modifier, with those considered depressed having higher rates of a MCI diagnosis (172). Similarly, Ailshire et al found neighborhood stress modified the effect of $PM_{2.5}$ on cognition, causing the effect of pollution to be greater in individuals living in high stress neighborhoods (148). In the NAS, Collicio et al assessed a series of genetic factors known to be associated with cognition to see if they would modify the effect of BC on cognition (150,160,177). They found that the presence of SNPs in miRNA-processing genes, longer blood telomere length, and several mitochondrial haplogroups modified the effect of BC on cognitive impairment. Within the HRS, interactions were tested between all covariates, with the finding that the only significant variable was smoking (174). In other studies, testing for interactions between a series of cardiovascular risk factors (166,180), and the APOE-ε4 allele (164) resulted in non-significant associations. Due to these limited results, future studies should pay special attention to potential effect modifiers largely to identify potentially vulnerable populations that may be at highest risk for harmful health effects due to air pollution.

DISCUSSION

Overall, the data shows evidence of association between ambient air pollution and poor cognitive function, although there is no clear pattern of association in the current research. This concept, however, is biologically plausible and has been illustrated in other areas of study. Several studies have illustrated the effect of air pollution and environmental toxins on the neurodevelopment of children, from time of prenatal exposure through adolescence (52,202–206). Research done on the cognitive effects of pollution on young children in Mexico City has shown that increased exposure causes cognitive deficits in several measures of cognitive performance, MRI-detected white matter lesions, and elevated levels of neuro-inflammatory markers in the brain (200,203–205). Studies have also shown that exposure to air pollution is associated with a decreased attention span (207), lower cognitive development and function (208–210), and gross motor function (206) in school-aged children.

Experimental animal studies have also described two key pathways through which pollutant particles reach the central nervous system (CNS), entering through the lungs and inducing a systemic response through the circulatory system or impacting the CNS directly intra-nasally by direct translocation the olfactory bulb (50,211–215). Once inside the CNS, pollutant particles activate a series of systemic inflammatory pathways leading to vascular inflammation (203,216,217), impaired microvascular reactivity (218), and changes in cerebral hemodynamics (219). Further validation of these mechanisms comes from studies done in Mexico City, where strong histological evidence of cerebral microvascular damage, systemic inflammatory markers, and brain pathology has been observed in autopsied brains of dogs and children residing in high vs. low pollutant areas (220–222). The influence of inflammation on the progression of neurodegeneration and cognitive decline has also been examined using animal models, identifying pathways through which an inflammatory response may mediate the effect of air pollution on cognitive decline (223). Rodents exposed to varying levels of diesel exhaust showed increased oxidative stress and systemic inflammation as exposures increased (224). These results were replicated in autopsies of highly exposed dogs (202,203,222,225).

In addition to what has been shown in animal studies, studies have suggested older adults are particularly vulnerable to the health effects of adverse environmental exposures, which cause amplified respiratory and cardiovascular symptoms, exacerbations of existing diseases, and increased mortality (55–57). Long-term exposure to pollution has been associated with increased risk of incident CVD (95,96,105), acute MI (104), heart failure (63,106), and death (97,114–118,120,121), with several large cohort studies highlighting the association between fine particulate matter exposure and overall CVD mortality (67,97–103). The effects of air pollution are also associated with several cardiovascular and cognitive risk factors including diabetes (123–125), total cholesterol and triglycerides (126), blood pressure (126–129), and C-reactive protein (130) which lends further biological and mechanistic plausibility to an ambient air pollution and cognition link.

As global life expectancy continues to increase, the rates of age-related cognitive decline and dementia are expected to skyrocket. The identification of novel risk factors, including ambient air pollution, is of great importance. The ability to reduce air pollutants on a population level makes it a very interesting modifiable risk factor, as the public health impact of any intervention could be substantial. There is some evidence that the health effects of ambient air pollution have been positively impacted by regulatory actions aimed at reducing levels of pollution over the last 30 years (97,118,122). A natural experiment done in Dublin, Ireland showed that after a ban in coal sales and subsequent decrease of black smoke concentration by 35.6 $\mu g/m^3$, overall non-traumatic death rates decreased by almost 6%. Larger decreases in mortality were seen in respiratory and cardiovascular deaths, with a reduction of 15.5% and 10.3%, respectively (122). Similarly, a decrease in mortality due to cardiovascular and respiratory disease was seen in the longitudinal Harvard Six Cities study, with drops in adjusted mortality rates largest in cities with the largest decreases in $PM_{2.5}$ (97).

The existing evidence is highly suggestive of an association between ambient air pollution and cognition, with all studies reporting at least one adverse association. It is clear, however, that these studies on cognitive function and decline have not been performed or analyzed in a homogenous way. There are substantial differences in study design, population, methodology, and measurement of both exposure and outcome that make direct comparisons across studies difficult and make it difficult to identify a true association. Identified data inconsistency and knowledge gaps speak to the need for comprehensive analyses with longitudinal data in order to begin to examine true trajectories of cognitive decline.

In order to begin to address the limitations of current studies and add to the knowledge base supporting the association between ambient air pollution and cognitive decline, I have brought together two prospective, population-based cohorts, the Northern Manhattan Study (NOMAS) and the Washington Heights Inwood Community Aging Project (WHICAP) to study the association between exposure to ambient air pollution and age-related cognitive decline.

The NOMAS and WHICAP cohorts included in this dissertation provide a unique opportunity to evaluate multi-dimensional data in a population of over 6,000 residents of Northern Manhattan. Neuropsychological (NP) batteries used in NOMAS and WHICAP are very similar; both were designed to capture key cognitive domains in both English and Spanish speaking older adults and developed to permit the calculation of z-scores that allow for measure of global cognition as well as cognitive domain-specific analyses. Additionally, serial NP testing allows for the analysis of cognitive decline over time. Several measure of long-term exposure to air pollution was measured using exposure estimates for $PM_{2.5}$, PM_{10}, and NO_2 generated from the Multi-Ethnic Study of Atherosclerosis and Air Pollution Study (MESA-Air). The use of several measures of pollution allowed for comparison across exposures and will attempt to identify a pattern of effect. Exposure status was assigned to participants based on reconstructed address histories, so as to mitigate potential measurement error, a common issue in current studies. In addition, these cohorts allowed for the assessment of effect measure modification by behavioral and genetic factors, and the identification of high risk groups. Using this uniquely qualified study population, **I first investigated the association between long-term exposure to ambient air pollution and cognitive decline among older adults in an urban population within Northern Manhattan.** I then set out to **assess specific mechanisms involved in the association between long-term exposure to ambient air pollution and cognitive decline, specifically investigating the APOE-ε4 allele, age, and current smoking behavior as effect modifiers of the association between long-term exposure to ambient air pollution and cognitive decline among older adults in an urban population within Northern Manhattan.**

TABLES AND FIGURES

Table 1.1 Database Search Terms	
PubMed	
Exposure	“Air Pollution”[Mesh] OR “Particulate Matter”[Mesh] OR “Nitrogen Dioxide”[Mesh] OR “nitrogen oxides[MeSH Terms]” OR “Ozone”[Mesh] OR “Sulfur Dioxide”[Mesh] OR “Carbon Monoxide”[Mesh] OR “Vehicle Emissions”[Mesh] OR “distance to road”[tw] OR “PM10” [tw] OR “PM2.5” [tw] OR “traffic-related air pollution” [tw] OR “air pollution” [tw] OR “particulate matter” [tw] OR “nitrogen oxide*” [tw] OR “ozone”[tw] OR “nitrogen dioxide”[tw] OR “particulates” [tw] OR “black carbon” [tw] OR “traffic pollution” [tw] OR “residential distance to nearest major”[tw] OR “traffic-related PM”[tw]
Outcome	“dementia”[mesh] OR “Alzheimer Disease”[mesh] OR “dementia”[tw] OR “Alzheimer”[tw] or “alzheimers”[tw] or “alzheimer’s”[tw]) OR “mild cognitive impairment” [MeSH] OR “cognitive decline” OR “neuropsycholog*” OR cognit* OR “cognitive change” OR “cognitive aging” OR “cognitive impairment” OR “neurobehavioral”
Exclusion	“children” OR “infant*” OR “pediatric*” OR “childhood” OR “adolescent*” OR “adolescence” OR “child*” OR “preschool” OR “prenatal” OR “smoking” OR “smoker*” OR “second hand smoke” OR “second-hand smoke”
EMBASE	
Exposure	‘air pollution’/de OR ‘air pollutant’/de OR ‘particulate matter’/exp OR ‘nitrogen dioxide’/exp OR ‘ozone’/exp OR ‘nitrogen oxides’/exp OR ‘sulfur dioxide’/exp OR ‘exhaust gas’/exp OR ‘distance to road’:ab,ti OR ‘pm10’:ab,ti OR ‘pm2.5’:ab,ti OR ‘traffic-related air pollution’:ab,ti OR ‘air pollution’:ab,ti OR ‘particulate matter’:ab,ti OR ‘nitrogen oxides’:ab,ti OR ‘ozone’:ab,ti OR ‘nitrogen dioxide’:ab,ti OR ‘particulates’:ab,ti OR ‘black carbon’:ab,ti OR ‘traffic pollution’:ab,ti OR ‘residential distance to nearest major’:ab,ti OR ‘traffic-related pm’:ab,ti
Outcome	‘dementia’/de OR ‘alzheimer disease’/de OR ‘frontotemporal dementia’/de OR ‘multiinfarct dementia’/de OR ‘presenile dementia’/de OR ‘senile dementia’/de OR dementia OR alzheimer* OR ‘mild cognitive impairment’/exp OR ‘mci’:ab,ti OR ‘cognitive decline’:ab,ti OR neuropsycholog*:ab,ti OR cognit*:ab,ti OR ‘cognitive change’:ab,ti OR ‘cognitive aging’:ab,ti OR ‘cognitive impairment’:ab,ti OR ‘neurobehavioral’:ab,ti

Exclusion	(children’ OR ‘infant’ OR ‘infants’ OR ‘pediatric’ OR ‘adolescent’ OR ‘smoking’ OR ‘smoker’ OR ‘second hand smoke’ OR ‘second-hand smoke’ OR ‘smokers’ OR ‘childhood’ OR ‘adolescents’ OR ‘adolescence’ OR ‘child’ OR ‘preschool’ OR ‘prenatal’):ti
PROQUEST Dissertation	
Exposure	"Air Pollution" [nesh] OR "Particulate Matter" [nesh] OR "Nitrogen Dioxide" [nesh] OR "nitrogen oxides[nesh Terms]" OR "Ozone" [nesh] OR "Sulfur Dioxide" [nesh] OR "Carbon Monoxide" [nesh] OR "Vehicle Emissions" [nesh] OR "distance to road" [taw] OR "PM10" [taw] OR "PM2.5" [taw] OR "traffic-related air pollution" [taw] OR "air pollution" [taw] OR "particulate matter" [taw] OR "nitrogen oxide*" [taw] OR "ozone" [taw] OR "nitrogen dioxide" [taw] OR "particulates" [taw] OR "black carbon" [taw] OR "traffic pollution" [taw] OR "residential distance to nearest major" [taw] OR "traffic-related PM" [taw]
Outcome	"dementia" [nesh] OR "alzheimer Disease" [nesh] OR "dementia" [taw] OR "alzheimer" [taw] OR "alzheimers" [taw] OR "alzheimer’s" [taw]) OR "mild cognitive impairment" [nesh] OR "cognitive decline" OR "neuropsycholog*" OR cognit* OR "cognitive change" OR "cognitive aging" OR "cognitive impairment" OR "neurobehavioral"
Exclusion	"children" OR "infant*" OR "pediatric*" OR "childhood" OR "adolescent*" OR "adolescence" OR "child*" OR "preschool" OR "prenatal" OR "smoking" OR "smoker*" OR "second hand smoke" OR "second-hand smoke"

Figure 1.1 Flow Chart of Study Selection Process

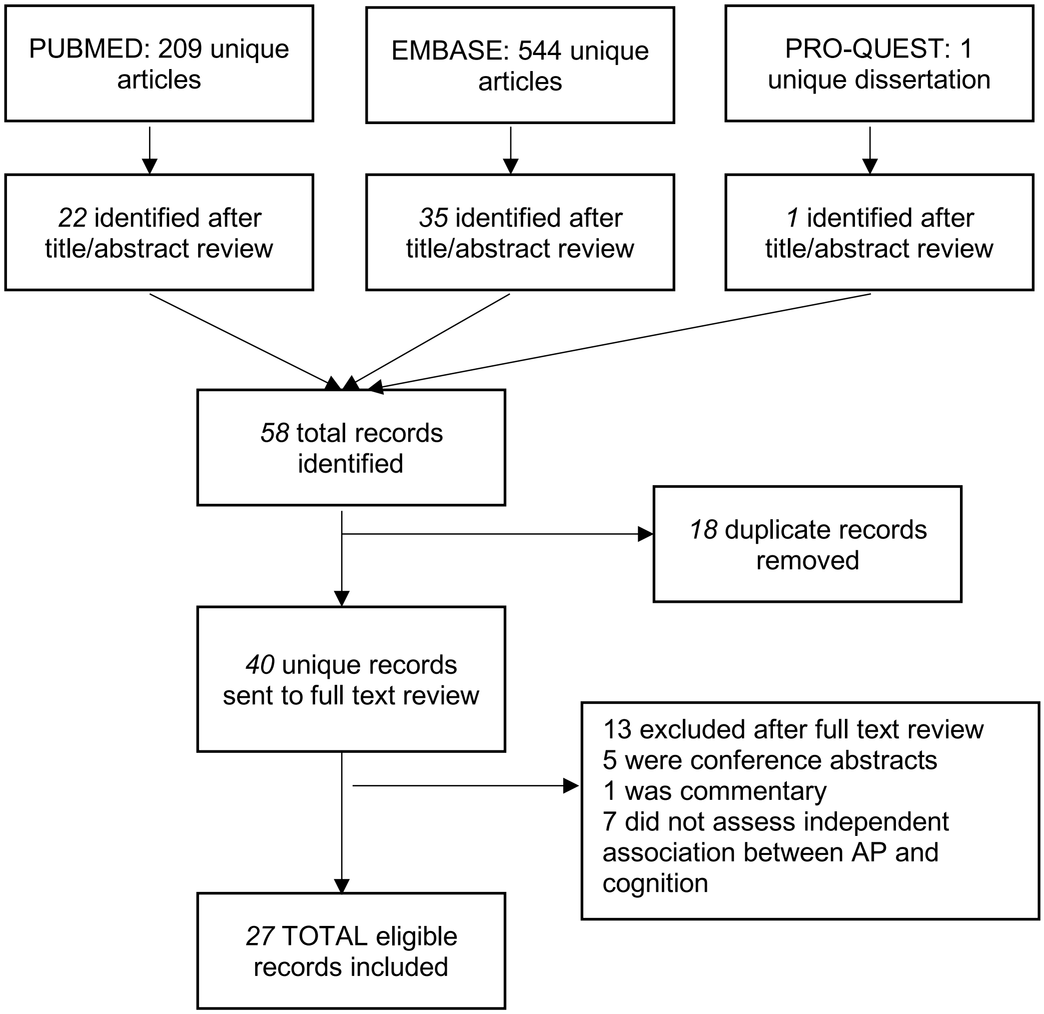

Table 1.2 Current studies examining the relationship between exposure to long-term ambient air pollution and cognition in older adults.

Author (ref)	**Study**	**Population Characteristics**	**Ambient Air Pollution Exposure**		**Measures of Cognition, *Tests***	**Confounders**	**Results**
			Pollutant, *geography*	**Levels**			
Ailshire and Crimmins, 2014 (174)	Health and Retirement Study (HRS), USA *Cross-sectional*	n= 13,996 Mean age: 61±10.4 56% Female 81%White	1 year average $PM_{2.5}$ *Census tract*	Quartiles of $PM_{2.5}$ (µg/m^3) 4.50–9.94 9.94–12.18 12.19–13.80 13.80–20.66	Cognitive Function *Episodic memory, mental status*	age, sex, race/ethnicity, education, employment, household income, smoking; census-tract level:: % residents without HS degree, median household income	Highest vs. lowest quartile of $PM_{2.5}$ exposure associated with decrease in episodic memory (-0.17l -0.33, -0.01), but was not associated with mental status (-0.09; -0.19,0.00)
Ailshire and Clark, 2015 (154)	American's Changing Lives (ACL) Study, USA *Cross-sectional*	n=780 Age: 49% 55-64 25% 65-74 19% 75-84 7% 85+ 61% Female 90% White	Averaged Annual $PM_{2.5}$ *Census tract*	$PM_{2.5}$ (µg/m^3): 13.8±3.1	Cognitive Function: Working memory and orientation *Errors of: Serial 3s subtraction, recall of date, day, president,*	age, gender, race, education, income, marital status, employment, residential tenure, neighborhood SES	A 10 µg/m^3 increase in $PM_{2.5}$ increased the incident rate of cognitive function errors by 1.5 (IRR= 1.53; 1.02,2.30), after adjustment for individual and neighborhood level characteristics.

					and vice president		
Ailshire et al., 2017 (148)	American's Changing Lives (ACL) Study, USA *Cross-sectional*	n=779 Mean Age (SD): 68 $\pm$ 9.8 61% Female 90% White	Averaged Annual $PM_{2.5}$ *Census tract*	$PM_{2.5}$ ($\mu g/m^3$): 13.8±3.1	Cognitive Function: Working memory and orientation *Errors of: Serial 3s subtraction, recall of date, day, president, and vice president*	age, gender, race, education, income, marital status, employment, residential tenure, neighborhood SES	A 10 $\mu g/m^3$ increase in $PM_{2.5}$ increased the incident rate of cognitive function errors by 1.04 (IRR= 1.04; 1.00, 1.08), after adjustment for individual and neighborhood level characteristics.
Chang et al., 2014 (169)	Taiwan National Health Insurance Research Database, Taiwan *Retrospective cohort*	n= 29,547 Mean age: 61.4±8.5 46% Female	NO_2 and CO, averages calculated from BL to event *Location of clinics of recruitment*	Quartiles of NO_2 and CO ($\mu g/m^3$) not defined	Dementia Diagnosis, defined by ICD-9 codes	age, sex, monthly income, DM, HTN, ischemic heart disease, COPD, alcoholism, urbanization	Highest quartile vs. lowest quartile of NO_2 associated with incidence of dementia (HR=1.54; 1.34-1.77). Adjusted HRs for the association of CO and incidence of dementia were significant when comparing Q3 and Q4 (HR=1.37; 1.19-1.58 and HR=1.61; 1.39-1.85), respectively.

Chen & Schwartz, 2009 (180)	Third National Health and Nutrition Examination Survey (NHANES), USA *Cross-sectional*	n= 1,764 Mean age: 37.4±10.9 50% Female 34% White	Annual average PM_{10} and O_3 levels *Census tract*	PM_{10} (μg/m^3): 7.2±12.8 O_3 (ppb): 26.5±5.2	Cognitive (CNS) Function *SRTT, SDST, SDLT*	age, sex, race/ethnicity, individual SES, family size, annual family income, poverty-income ratio, urban/rural residence smoking, alcohol consumption, exercise, BMI, DM, HTN, treatment for HTN, HDL, Indoor air pollution	10 μg/m^3 increase in PM_{10} not significantly associated with cognitive function. SRTT (β=-0.36, -2.58 to 1.85); SDST (β=0.00, -0.04 to 0.05); SDLT trials to criterion (β=0.09, 0.00 to 0.17); SDLT total (β=0.12, -0.07 to 0.31). 10 ppb unit increase in O_3 associated with SDST (β=0.12, 0.01 to 0.23); SDLT trials to criterion (β=0.28, 0.06 to 0.51); SDLT total (β=0.57, 0.0-1.06), but not SRTT (β=-0.92, -6.45 to 4.61).

Chen et al., 2017 (155)	Ontario Population Health and Environment Cohort (ONPHEC) *Prospective Cohort*	n= 2,066,639 Mean age (SD): 66.8 $\pm$ 8.2 53% Female	Averaged annual $PM_{2.5}$, NO_2, and O_3 for each year between 1994-2013 *Residential postal code*	$PM_{2.5}$ ($\mu g/m^3$): 10.4 (IQR: 4.8) NO_2 (ppb): 16.2 (IQR: 14.2) O_3 (ppb): 45.8 (IQR: 6.3)	Incident dementia diagnosis *$\geq$ Hospital admission with diagnosis of dementia, 3 physician claims for dementia, or a prescription relating to dementia.*	Age, sex, preexisting comorbidities (TBI, diabetes, HTN, stroke, CHD, CHF, arrhythmia), baseline SES, neighborhood level variables (income quartile, education, unemployment rate, % of recent immigrants, neighborhood level deprivation, urban residence, density of physicians), Toronto vs. all other areas.	An IQR increase in $PM_{2.5}$ increased the incident rate of dementia by 4% (HR_{iqr}: 1.04; 1.03-1.05) in fully adjusted models. NO_2 associated with 10% higher incidence of dementia (HR_{iqr}: 1.10; 1.08-1.12) No significant association found between O_3 and incident dementia. (HR_{iqr}: 0.98; 0.96,1.00)
Chen et al., 2017 (144)	Ontario Population Health and Environment Cohort (ONPHEC) *Prospective Cohort*	n= 2,165,268 Mean age (SD): 66.8 $\pm$ 8.2 53% Female	Residential proximity to major roadways; secondary exposures $PM_{2.5}$, NO_2 *Residential postal code*	50% living within 200m, 95% live within 1000m. $PM_{2.5}$ ($\mu g/m^3$): 9.7 (range 1.3-19.8)	Incident dementia diagnosis *$\geq$ Hospital admission with diagnosis of dementia, 3 physician claims for*	Age, sex, preexisting comorbidities (TBI, diabetes, HTN, stroke, CHD, CHF, arrhythmia), baseline SES, neighborhood level variables (income quartile,	Fully adjusted HR 1·07 (95% CI 1·06–1·08) for people living less than 50 m, 1·04 (1·02–1·05) for people living 50–100 m, 1·02 (1·01–1·03) for people living 101–200 m, and 1·00 (0·99–1·01)

				NO_2 (ppb): 15.4 (range 1.1-62.0)	*dementia, or a prescription relating to dementia.*	education, unemployment rate, % of recent immigrants, neighborhood level deprivation, urban residence, density of physicians), Toronto vs. all other areas.	for people living 201–300 m away from a major roadway versus more than 300 m from a major roadway. $PM_{2.5}$ and NO_2 were both significantly associated with incident dementia.
Colicino et al., 2014 (150)	VA Normative Aging Study (NAS) *Cross-sectional*	n= 582 Mean age (SD): 72 $\pm$ 7 100% Male 100% White	Yearly Average of Black Carbon (BC) *Participants geocoded residence*	1-yr average ln(BC) exposure estimates mean $\pm$ SD: 0.6 $\pm$ 0.6 range (0.03 to 1.77 $\mu g/m^3$)	Cognitive Change *MMSE at each time point and change between assessments*	Age, education, alcohol use, physical activity, diabetes, fish consumption, computer experience, language, time of cognitive assessment, neighborhood (% non-white, % residents with college degree, Boston vs. non-Boston)	Each doubling of BC on a natural scale was associated with 1.22 times higher odds (95% CI 0.95-1.56) of low MMSE Score adjusted for clinical and lifestyle factors.

Colicino et al., 2016 (177)	VA Normative Aging Study (NAS) *Cross-sectional*	n= 533 Mean age (SD): 72 ± 7 100% Male 100% White	Yearly Average of Black Carbon (BC) *Participants geocoded residence*	1-yr average ln(BC) exposure estimates mean ± SD: 0.51 ± 0.26 range (0.02 to 1.9 μg/m^3)	MMSE and Global Cognitive Function *MMSE, digit span backward test, verbal fluency test, constructional praxis, immediate and delayed recall of 10 word test, pattern comparison test*	Age, education, alcohol use, physical activity, diabetes, fish consumption, computer experience, language, time of cognitive assessment, neighborhood (% non-white, % residents with college degree, Boston vs. non-Boston)	Each doubling of BC on a natural scale was associated significantly elevated risk (IR: 1.50; 95% CI 0.95-1.56) of low MMSE Score adjusted for clinical and lifestyle factors. BC not significantly associated with global cognitive function score.
Colicino et al., 2016 (160)	VA Normative Aging Study (NAS) *Cross-sectional*	n= 428 Mean age (SD): 73.6 + 6.6 100% Male 100% White	Yearly Average of Black Carbon (BC) *Participants geocoded residence*	1-yr average BC exposure estimates mean ± SD: 0.46 ± 0.23 range (0.02 to 1.9 μg/m^3)	Cognitive Change *MMSE at each time point and change between assessments*	Age, education, alcohol use, physical activity, diabetes, fish consumption, computer experience, language, time of cognitive assessment, neighborhood (% non-white, % residents with college degree,	BC exposure was significantly associated with higher relative odds of low MMSE scores. A doubling of BC concentration during the previous year was associated with 1.57 times (95% CI; 1.20-2.05) higher relative odds of low MMSE Scores based on

						Boston vs. non-Boston)	fully adjusted model.
Gatto et al.,2014 (178)	Participants recruited from three RCTs at the University of Southern California, USA *Cross-sectional*	n=1,496 Mean age: 60.5±8.1 79% Female 66% White	8-hour O_3, 24-hour $PM_{2.5}$ and NO_2 measured through geocoding of local air monitoring data *Residential geocoded address*	Categories of Exposure O_3 (ppb): 34, 34-49, >49 $PM_{2.5}$ (µg/m^3): 15. 15-17,>17 NO_2 (ppb): 10, 10-20, >20	Cognitive Function *Executive function, verbal learning, logical memory, visual processing, episodic& semantic memory*	age, race/ethnicity, gender, education, household income, depression, indicator term for fixed effect of study	No significant association between pollutant exposure and global cognition score, comparing highest level to lowest level of pollutants showed overall reduction. O3: β=-0.08; 0.45, 0.28; No2: β=-0.32; -0.92, 0.28; PM: β=-0.15; -0.39,0.08. $PM_{2.5}$ >17 µg/m^3 significantly associated with lower verbal learning scores (β= -0.37; -0.64, -.010)

Jung et al.,2015 (168)	Taiwan National Health Insurance Research Database, Taiwan *10 year prospective cohort*	n= 95,690 Age: 24% 65-69 24%70-73 27%74-79 24% ≥80 46% Female	Annual averages $PM_{2.5}$, O_3 measured at BL and time of event *Post-code*	Baseline $PM_{2.5}$ ($\mu g/m^3$): 34.4±8.6 Baseline O_3 (ppb): 89.0±7.8	Diagnosis of Alzheimer Disease ICD-9 diagnosis	age, gender, income, diabetes, hypertension, MI, angina, stroke, PAD, asthma, COPD	A 9.63 ppb increase in O_3 at BL was associated with increased rate of incident AD (HR=1.06; 1.00–1.12); with every 10.91 ppb increase from BL to event, the rate of AD increased by 211% (2.92,3.33). At BL, $PM_{2.5}$was not significantly associated with AD, however for every 4.34 $\mu g/m^3$ increase in $PM_{2.5}$ over follow-up the risk of AD increased by 138% (2.21–2.56).
Kioumourtz-oglou et al., 2015 (170)	Medicare Enrollees from 50 cities across the Northeastern United States, USA *Prospective Cohort*	n= 9.8 mil Mean age (SD): 75.6 ±7.6 57% Female 80% White	Annual concentrations of $PM_{2.5}$ from 1999-2010 *City*	$PM_{2.5}$ ($\mu g/m^3$): 12.0±1.6 IQR 3.8	Diagnosis of Parkinson's disease, dementia, or Alzheimer disease *ICD-9*	age, sex, race, CHF, MI, COPD, DM, zip code, census-tract median income	A 1 $\mu g/m^3$ increase in city-wide $PM_{2.5}$ was associated with a 8% increase in PD admissions (HR=1.08;1.04,1.12); a 15% increase in AD admissions (HR=1.15;1.11,1.19); and an 8% increase in dementia

							admissions (HR=1.08; 1.05,1.11)
Loop et al., 2013 (181)	REGARDS Cohort, USA *Cross-sectional*	n=20,150 Mean age: 64.3 ± 9 56.3% Female 60.1% White	1 year average $PM_{2.5}$ *Residential geocoded address*	Quartiles of $PM_{2.5}$ ($\mu g/m^3$): 6.6-12.2 12.2-13.6 13.6-14.8 14.8-21.0	Incident Cognitive Decline *SIS*	age, sex, race, region, income, education, depression, smoking, alcohol use, exercise, SBP, DBP, lipid levels, BMI, HDL, HTN, DM, stroke, temperature, season	A 10 $\mu g/m^3$ increase in $PM_{2.5}$ was not associated with odds of incident cognitive impairment after adjustment for confounders (OR=1.26; 0.97,1.64)
Oudin et al., 2016 (171)	Betula Study, Sweden *Prospective Cohort*	n= 1,806 Age: evenly distributed among 10 age cohorts from 35-80 57% Female	Annual average NO_x estimated for participants at BL *Residential geocoded address*	Quartiles of NO_x ($\mu g/m^3$): 4.8-9, 9-17, 17-26, >26	Diagnosis of dementia, Alzheimer disease, and VaD *Betula Cognitive test battery*	age, sex, education, physical activity, smoking, alcohol, BMI, waist-to-hip ratio, HTN, DM, stroke, APOE4	NO_x highest vs. lowest quartile of exposure associated with 60% increase in rate of dementia (HR=1.6; 1.02, 2.10) in fully adjusted models. NO_x was not associated with an increased rate of AD or VaD.

Power et al., 2011 (158)	US Department of Veterans Affairs Normative Aging Study (NAS), USA *12 year prospective*	n= 680 Mean age: 71±7 0% Female 100% White	Annual average BC concentration in year prior to cognitive assessment *Residential geocoded address*	BC ($\mu g/m^3$): 0.58±0.28	Global Cognitive Function *MMSE; digit span backwards test, verbal fluency, constructional praxis, immediate & delayed recall, pattern comparison task.*	age, education, alcohol use, physical activity, diabetes, fish consumption, computer use, language, % census tract non-white, % census tract college degree, time of cognitive assessment indicator, residence in Boston	Each doubling of BC associated with increased odds of having MMSE $\leq$ 25 (OR=1.3; 1.1,1.6); and lower global cognitive function (-0.054 SD lower test score, -0.103, -0.006)
Ranft et al., 2009 (179)	Study on the Influence of Air Pollution on Long Function, Inflammation, and Aging (SALIA), Germany *Cross-Sectional*	n= 402 Mean age: 74.1±2.6 100% Female	5 year average PM_{10}; distance to major roadway, at baseline and time of cognitive assessment *Residential geocoded address*	PM_{10} ($\mu g/m^3$) Baseline: 45.0- 48.6 Assessment: 25-28.3	Cognitive Function *CERAD-PLUS; Stroop test, sniffing sticks*	age, education, physical activity, obesity, smoking, environmental tobacco smoke, indoor air pollution, depression, bronchitis, COPD, DM, HTN, HDL, MI, stroke	Living within 5-m of a high traffic road associated with CERAD-plus (β=-3.8, -7.8 to 0.1); Stroop (β=-5.1, -8.2 to -2.0), Sniffing (β=-1.3, -2.4 to -0.2) in women $\leq$ 74 years old. No significant adverse effect in women > 74 years old.

							No significant associations between PM_{10} at baseline and cognition (CERAD-plus (β=0.4, 0.0 to 0.9); Stroop (β=-0.0, -0.4 to 0.4); Sniffing (β=0.0, -0.1 to 0.1)) or at time of cognitive assessment (CERAD-plus (β=-0.6,-1.4 to 0.2); Stroop (β=0.2, -0.4 to 0.7); Sniffing (β=0.1, -0.1 to 0.3)).
Schikowski et al., 2015 (164)	SALIA, Germany *Cross-sectional*	n=789 Mean age: 73.4±3.1 100% Female	Annual averages NO_2, NO_x, $PM_{2.5}$, PM_{10}, Daily traffic load within 10m of residence, at BL and FU	Median(IQR) NO_2 (µg/m^3) BL:50.2 (7.1) NO_x(µg/m^3) BL:60.6 (43.1) $PM_{2.5}$ (µg/m^3) BL:33.3(4.7)	Global Cognition *CERAD-plus, MMSE*	smoking, ETS, education, physical activity , COPD, bronchitis, HTN, MI, stroke, BMI, depression, medication use	Overall positive association between increased pollution levels and lower cognitive function, however results non-significant overall. Only increased change in NO_x significantly associated with lower CERAD score (β=-1.35; -2.59, -0.10)

			Residential geocoded address	PM_{10}(μg/m^3) BL:50.2(7.1) Traffic Load: BL: 212 (26.9)			
Semmens, 2012 (132) *	Cardiovascular Health Study (CHS), USA *Longitudinal*	n= 3,212 Mean age: 74±5 56% Female 78% White	PM_{10}, NO_2, yearly averages after entry into CHS, modeled as time-dependent exposure *Residential geocoded address*	Averages of PM_{10} (μg/m^3) 1 Yr: 35 ± 5 2 Yr: 35 ± 5 3 Yr: 34 ± 4 4 Yr: 33 ± 4 Averages of NO_2 (ppb): 1 Yr: 21 ± 5 2 Yr: 21 ± 5 3 Yr: 21 ± 5 4 Yr: 21 ± 5	Cognitive Function *3MSE, DSST*	age, gender, race, education, income, BMI, physical activity, physical function, depression, smoking status, alcohol use, stroke, TIA, HTN, DM, MI, CHF, APOE gene	A 10 µg/m3 increase in PM_{10} associated with -2.6 (-3.1, -1.5) decrease in 3MSE score, but not with a decrease in DSTT score (β=-1.1, -2.2,0.1). A 5-ppb increase in NO_2 associated with significant decreases in both 3MSE (β=-2.8, -4.0,-1.6) and DSST (β=-2.0, -3.0,-0.9) scores.
		n= 3,602 Mean age:81 ±4 57% Female 96% White			Validated clinical diagnosis of MCI or dementia (subtyped: AD, VaD,		No significant associations between 1,2, or 3 year average PM_{10} or NO_2 exposure and prevalent dementia or AD. Significant

					mixed AD/VaD)		association between 1 and 2 year average PM_{10} and prevalence of VaD (OR=1.71; 1.00,2.92 ; OR=2.08; 1.02,4.24). All associations between a 10 μg/m^3 elevation of PM_{10} and incident dementia (including subtypes) were null.
Sun & Gu, 2008 (165)	Chinese Longitudinal Health Longevity Survey, China *Cross-sectional*	n= 7,358 Mean age: 86.3±11.4 57% Female	Annual API *City*	Mean API 3.5±1.19	Cognitive Function *MMSE*	age, gender, ethnicity, education, occupation, perceived family economic conditions, marital status, number of living children, smoking, alcohol use, physical activity, leisure activities, average temperature	1-point increase in API associated with a 0.51 increase in MMSE score (95% CI 0.27-0.75)
Tallon et al., 2017 (151)	National Social Life and Aging	n= 3,374 Mean age ± SD: 72.3 ± 8.1	1-7 year moving averages	1-yr moving average (IQR) for	Global Cognition	Age, race, ethnicity, gender, education,	IQR increase in both 1 and 7 year $PM_{2.5}$ associated

	Project (NSHAP) *Cross-sectional*	50% Female 72% White	calculated from daily values of $PM_{2.5}$ and NO_2 *Participants geocoded residence*	$PM_{2.5}$ 10.23 (2.5) and NO_2 10.13 (6.28)	*Chicago Cognitive Function Measure (CCFM)*	season, smoking status, geographic region, median household income of census tract, BMI, MP, HbA1c, CRP, ADLs, emotional health, social connectedness, loneliness, depression, anxiety, and stress.	with reduction in CCFM scores in fully adjusted models, highest effects at 7 years (−0.25, 95% CI:−0.43,−0.06). Similar IQR increases in 2 year (−0.26, 95% CI:−0.45,−0.06) to 7year(−0.27, 95% CI:−0.48,−0.07) moving averages of NO_2 exposures were also associated with decreased CCFM scores in fully adjusted models
Tonne et al., 2014 (176)	Whitehall II Cohort Study, UK *5 year longitudinal*	n= 2,867 Mean age: 66 ± 6 35% Female 86% White	Annual average $PM_{2.5}$, PM_{10} measured over 1,3,5 years prior to testing *Post-code center*	PM_{10} ($\mu g/m^3$) 1yr:21.5±1.6 3yr:24.2±1.5 5yr:23.4±1.5 $PM_{2.5}$ ($\mu g/m^3$)	Reasoning, short-term memory, verbal fluency *Alice Heim 4-1 Test, 20-word free recall, verbal fluency*	age, sex, ethnicity, marital status, education, socioeconomic position, smoking status, alcohol use, fruit/vegetable consumption, physical activity, SBP, DBP, serum cholesterol	Five-year average exposures were consistently associated with all measured components of cognitive decline, however no associations were significant.

				1yr:13.1±0.9 3yr:15.7±0.9 5yr:14.9±0.9		levels, stroke, CHD, DM, depression.	
Tzivian et al., 2016 (172)	Heinz Nixdorf Recall Study, Germany *Cross-sectional*	n= 2,050 Mean age: 64±7.7 51% Female	Annual Averages PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$, NO_x, and NO_2. *Residential geocoded address*	Mean (μg/m^3) PM_{10}:27.7±1.8 $PM_{10-2.5}$: 10.1±1.5 $PM_{2.5}$:18.4±1.1 NO_x: 50.5±12 NO_2:30.1±4.9	Cognitive Assessment and MCI diagnosis *Peterson MCI criteria, verbal memory, problem solving, processing speed, verbal fluency, abstraction*	age, sex, education, alcohol use, smoking, ETS, physical activity, depression, BMI, CHD, LDL-cholesterol, DM, HTN, APOE genotypes	An IQR increase in $PM_{2.5}$ associated with overall MCI (OR=1.16; 1.05,1.27) and amnestic MCI (OR=1.22; 1.08,1.38). IQR increases in PM_{10} (OR= 1.17; 1.07,1.35) and NO_2 (OR=1.13;1.01,1.38) were also associated with amnestic MCI. No exposures were significantly associated with non-amnestic MCI.
Weuve et al., 2012 (173)	Nurses Health Study Cognitive Cohort	n=19,409 Age: 74±2.3 100% Female	Average $PM_{2.5}$ and $PM_{2.5-10}$ in Month, 1yr, 2yr, 5yr, since	Mean $PM_{2.5}$ (μg/m^3) Month:12.5±4 1yr:12.7±3 2yr:13.1±3	Cognitive Function *TICS, East Boston Memory Test*	age, education, husband's education, physical activity, alcohol use, BMI, DM,	$PM_{2.5}$ and $PM_{2.5-10}$ highest vs. lowest quintile of exposure from baseline associated with greater 2 year

	(NHS), USA *7-13 year prospective*		BL preceding assessment *Residential geocoded address*	5yr:13.1±3 BL:14.2±3 Mean $PM_{2.5-10}$ (μg/m^3) Month: 8.6±5 1yr:8.3±4 2yr:8.2±4 5yr:8.5±4 BL:9.6±4		smoking, aspirin use, ibuprofen use	decline in global cognition (0.018; -0.034, -0.002 and -0.024; CI -0.040, -0.008). Higher exposure to $PM_{2.5-10}$ in the 1-5 years prior to assessment associated with significantly worse 2 year change in global cognitive score. Only $PM_{2.5}$ exposure at baseline period (from 1988) associated with 2-year change on cognitive score (-0.018; -0.035,-0.002).
Wellenius et al., 2012 (175)	MOBILIZE Boston Study, USA *17 year prospective*	n=765 Mean age: 78.1± 5.4 64% Female 77.5% White	Distance to major roadway; Average annual BC one year prior to assessment; *Residential geocoded address*	Average distance: 0-3 km Median (IQR) BC (μg/m^3): 0.36 (0.11)	Global Cognitive Function *MMSE, HVLT-R, TMT, Verbal Fluency, Clock in a Box*	age, sex, race, stroke, smoking, physical activity, education, BMI, income, season, census track level indicators of SES (% pop non-white and % pop with college degree)	An IQR decrease in distance to major roadway (mean change) associated with several cognitive tests: HVLT immediate recall (-0.6; -1.1,-0.1); HVLT Delayed recall (-0.4;-0.7,-0.1); Letter fluency (-1.4; -2.7,-0.2); Category

							fluency (-0.7;-1.1,-0.3); TMT part B time (10.5; 4.0, 17.1); TMT interference time (7.5, 2.2,12.8). An IQR decrease associated with MMSE <26 only in those older than 77 (OR: 1.34; 1.01–1.76) An IQR increase in BC associated with having MMSE < 26 (OR=1.15; 0.99,1.34) and diminished HVLT-R (β = -0.36; -0.71, -0.01)

Abbreviations: 3MSE – Modified Mini Mental State Examination; AD – Alzheimer Disease; API – Air Pollution Index calculated from concentrations of PM, O_3, CO, SO_2, NO_2 ;BC – Black Carbon; BL – Baseline; BMI – Body Mass Index; CERAD – Consortium to Establish A Registry for Alzheimer Disease; CHF – Congestive Heart Failure; COPD – Chronic Obstructive Pulmonary Disease; DBP – Diastolic Blood Pressure; DM – Diabetes ; DSST – Digit symbol substitution test ; ETS – Environmental Tobacco Smoke; FU – Follow-up; HR – Hazard Ratio; HS – High School; HDL – High-density lipoprotein; HTN – Hypertension; HVLT – Hopkins Verbal Learning Task-Revised; IQR – Interquartile Range; MCI – Mild Cognitive Impairment; MI – Myocardial Infarction; MMSE – Mini Mental State Examination; NO_2 – Nitrogen Dioxide; NO_x – Nitrogen Oxides; O_3 – Oxone; OR – Odds Ratio; PAD – Peripheral Artery Disease; PD – Parkinson's Disease; PM – Particulate Matter; SBP – Systolic Blood Pressure; SDLT – Serial-Digit Learning Test; SDST – Symbol Digit Substitution Test; SES – Socioeconomic Status; SIS – Six item screener; SRTT – Simple Reaction Time Test; TIA – Transient Ischemic Attack; TICS – Telephone Interview for Cognitive Status; TMT – Trail Making Test; VaD – Vascular Dementia

*For the purpose of evaluating the current research, I considered two chapters of this dissertation to be two separate analyses/papers, with different study components and results.

CHAPTER TWO.

Long-term Exposure to Ambient Air Pollution and Trajectories of Cognitive Decline in Northern Manhattan

INTRODUCTION

Age-related cognitive decline is a growing public health concern as increases in life expectancy are expected to substantially increase the prevalence of cognitive impairment and dementia (226). An estimated 46.8 million individuals are living with dementia, with the global prevalence expected to double every 20 years (1). Poor cognitive function is a key cause of disability among older adults and can have profound social, economic, and health implications (139,227). Global healthcare expenditures for cognitive impairment reached 818 billion dollars in 2015 and are expected to reach a staggering two trillion dollars by 2030 (1). Risk of accelerated cognitive decline increases with age, cerebrovascular disease, and the presence of traditional cardiovascular risk factors, but these factors do not fully account for risk of cognitive decline in the population. Identification of novel risk factors is therefore of great importance. Long-term exposure to ambient air pollution has recently been highlighted as a risk factor for cognitive decline in addition to its association with other cardiovascular and neurological outcomes (166,173,175).

Air pollution, a largely ubiquitous environmental exposure, is rapidly becoming a widespread public health hazard, particularly in urban areas. Despite significant decreases in overall levels of ambient air pollution over the last decade, levels remain high. As of 2011, 124 million United

States residents were living in areas that did not meet the US Environmental Protection Agency (EPA) National Ambient Air Quality Standards (49). While only recently implicated as a modifiable risk factor for cognitive decline, the concern over adverse health effects of air pollution is not new.

Studies have suggested older adults are particularly vulnerable to the health effects of adverse environmental exposures, which can cause amplified respiratory and cardiovascular symptoms, exacerbations of existing diseases, and increased mortality (55–57). Long-term exposure to pollution has been associated with increased risk of incident cardiovascular disease (CVD) (95,96,105), acute myocardial infarction (MI) (228), heart failure (63,106), and death (97,114–118,120,121), with several large cohort studies highlighting the association between fine particulate matter exposure and overall CVD mortality (67,97–103). The evidence linking air pollution with the cardiovascular and cerebrovascular systems suggest it may also have a damaging impact on the brain and cognitive processes, but research on the effects of pollution on the nervous system, particularly in older adults, is limited (136–138). Therefore, I set out to evaluate the association between long-term exposure to ambient air pollution and cognitive decline among older adults in an urban population within Northern Manhattan. I hypothesize that individuals exposed to higher levels of ambient air pollution will have steeper trajectories of cognitive decline.

METHODS

Data collection

The Northern Manhattan Study (NOMAS). NOMAS is an ongoing, prospective, population-based cohort study of 3,298 participants in a stroke-free multi-ethnic urban population. Initial eligibility for the cohort included those aged ≥ 40 years, a permanent resident of one of the 5 zip codes representing Northern Manhattan, lived in a house with a telephone, and no history of clinical stroke. Cohort recruitment occurred from 1993 to 2001 at which time participants were invited for an in-person baseline interview and health assessment for risk factors of stroke and cardiovascular disease (229,230). All interviews are conducted by trained bilingual interviewers in the primary language of the participant. NOMAS participants were recruited during annual follow-up to participate in a MRI sub-cohort if they met the following eligibility criteria: free of clinical stroke, free of clinically identified dementia, aged ≥50 years, and had no contraindications to MRI. A total of 1,091 participants were enrolled from 2003-2008. In addition, a sample of household members of NOMAS participants (n=199) were enrolled using the same eligibility criteria from 2006-2008 in order to increase sample size, creating a final non-demented MRI cohort sample of 1,290. Those participating in the MRI cohort underwent a standardized medical exam to ascertain risk factor status, MRI, and detailed neuropsychological (NP) exam at time of enrollment. Follow-up NP testing at a 5-year interval was completed on approximately 85% (n=989) of the surviving MRI cohort.

The Washington Heights Inwood Community Aging Project (WHICAP). WHICAP was established in three recruitment waves: 1992 (n=2234), 1999 (n=2180), and 2010 (n=2125). Detailed sampling strategies and recruitment outcomes have been discussed previously (231,232). The first wave of participants was recruited in 1992 from a random sample of Medicare-eligible adults (age ≥65) residing in the neighborhoods of Washington-Hamilton Heights and Inwood in Northern Manhattan. Of 4865 individuals invited to participate, 2125 (44%) were enrolled if they met inclusion criteria, still lived in Northern Manhattan, and spoke English or Spanish. The population comprised individuals from several countries of origin representing three broadly defined racial/ethnic categories (i.e., Caribbean Hispanic, black, non-Hispanic white). A randomly selected portion of the 1992 cohort underwent a standardized medical, neurologic, and neuropsychological examination (231). The second and third waves were recruited from the same community, with a goal to recruit a cohort of ethnically and educationally diverse non-demented elderly. These cohorts were not randomly identified, but instead chosen based on the following criteria: (1) the final sample would be equally divided among Hispanics, non-Hispanic blacks, and non-Hispanic whites, (2) the cohort would represent equal proportions of 65-74 and ≥ 75 year olds, and (3) individuals would be excluded if they had significant cognitive problems or had been diagnosed with having dementia. To date, at least one NP battery has been collected on 6,261 older adults, of which 13% had signs of dementia at baseline, leaving a final sample size of 5,478 non-demented individuals. Participants are evaluated longitudinally every 18-24 months, with a comprehensive NP battery, medical and neurological examination, and survey about lifestyle factors, medication, comorbidities, and risk factors.

Combination of Prospective Cohorts. A single analytical cohort was created by combining the NOMAS and WHICAP populations into a single prospective analytical cohort. The source populations from both studies were similar, and cohorts were recruited from overlapping neighborhoods in Manhattan, therefore I first set out to identify individuals who were participating in both cohorts. To do this, I matched individuals across the two cohorts using a combination of identifying features. Individuals were matched on four identifying characteristics: date of birth, sex, name, and race/ethnicity. Individuals who matched on all four characteristics were automatically linked and identified as being in both cohorts; those with 2 or 3 matching factors were hand matched to identify overlap. Individuals with less than 2 matching factors were automatically considered to be non-overlapping. In all, there were 240 individuals that were participants in both cohorts. All available cognitive assessments were used for the overlapping individuals.

The final analytical sample was comprised of individuals from both cohorts that were: (1) free of dementia at baseline, (2) have at least one NP examination at any point during the study period, (3) had primary addresses in NYC at time of baseline NP Examination due to availability of air pollution exposure models, (4) did not having missing data for any of the exposure or confounding variables, and (5) had enough non-missing NP data to calculate a global cognitive score. These exclusion criteria resulted in a total sample size of 6,206 individuals (Appendix Figure A.1).

All activities pertaining to NOMAS and WHICAP were approved by the Institutional Review Board at Columbia University Medical Center. Written consent was provided by each participant at enrollment

Assessment of Ambient Air Pollution. Participants' residential addresses were collected at each longitudinal follow-up and when available, address histories were reconstructed for baseline and at each NP assessment. Participants were classified as 'non-movers' if they were identified as not having moved throughout the study period, and 'movers' if they had different addresses at baseline and time of last NP exam. In this combined cohort, 90.6% of participants with available data were non-movers (n=2,339). A total of 3,625 of all participants (58%) had only one available address due to data collection procedures and could not be categorized into 'movers' vs. 'non-movers'.

Primary analyses used all individuals in both cohorts, and sensitivity analyses were performed by limiting analyses to non-movers only in order to ascertain the potential for measurement error due to changing residential locations. Residential addresses were geocoded using Geosupport Batch Address Translator Desktop Edition (NYC Department of City Planning, NY, NY). Only participants with primary addresses in New York City at the time of last NP exam were included in the analysis due to availability of air pollution exposure models.

Prior research in the NOMAS cohort identified the average pollutant level for 1 year to be a valid marker of long-term pollution (135), so estimates of residential air pollution exposure one year prior to baseline NP were ascertained using models developed for the Multi-Ethnic Study of

Atherosclerosis and Air Pollution Study (MESA-Air), as previously described (233–236). Ambient concentrations of fine particulate matter less than 2.5 µm in diameter ($PM_{2.5}$; µg/m^3), coarse particulate matter (PM_{10}; µg/m^3), and nitrogen dioxide (NO_2; ppb) were estimated for each address. MESA-Air pollution models utilized monitoring data from the U.S. EPA Air Quality System, monitors placed by MESA-Air at sites throughout the New York City area, and at MESA participants' homes. In addition, models included geographic covariates (roadway density, population density, urban land, agricultural land, forests, bodies of water), and outputs from dispersion models to improve predictions. These models permit characterization of seasonal time trends, key sources of spatial variability within the study area, and underlying spatial and spatiotemporal correlation. All exposures were obtained and analyzed as continuous variables and included in models per inter-quartile range (IQR).

Distance from participant residence to the nearest major roadway was calculated as a secondary marker of long-term exposure to traffic pollution. ArcGIS (version 10.3.1, ESRI, Inc., Redlands CA) was used to calculate the Euclidean distance from geocoded residence to nearest major roadway, defined as US Census Features Class A1 (primary highway with limited access) or A2 roadway (nationally and regionally important highways that do not have limited access), which include most federal and interstate highways and some larger state and county highways. Residential distance to roadway was modeled as a log-transformed continuous variable (per interquartile range (IQR)) based on prior studies (90,135).

Outcome Ascertainment. NP batteries used in NOMAS and WHICAP were very similar; both were designed to capture key cognitive domains in both English and Spanish speaking older adults and developed to permit the calculation of domain-specific Z-scores that allow for efficient cross-cohort harmonization for combined analysis due to a large number of overlapping tests (Table 2.1). Cognitive decline was measured in two ways: (1) trajectories of change in global cognition scores and (2) trajectories of performance in individual cognitive domains.

In order to utilize all available NP data for each cohort, I harmonized available tests across the two studies. All NP tests were first standardized into z-scores using combined cohort-specific means and standard deviations at baseline. I chose not to adjust for age, education, or race/ethnicity as done in prior studies so that these variables can be analyzed as confounders in order to be able to ascertain the independent effects of these covariates on cognition. Exploratory factor analyses had been performed previously in each of the individual cohorts to identify cognitive functional domains (14,231,237). To confirm that the NP data from this combined cohort still fit into the previously identified factor structure, I performed a confirmatory factor analysis (CFA) identifying four key functional domains (Appendix Table A.1). Performance in each of these four identified domains was expressed as the weighted mean of the individual test z-scores loading into that domain. Weights were calculated using the factor scores of the CFA. A global cognition score was constructed using the weighted mean of the z-scores of all NP tests used to calculate the functional domains and was used as the primary outcome to summarize the overall association of air pollution exposure on cognitive performance. When analyzing the processing speed domain, I found that the adjusted models did not converge, due to a large amount of missing data in the NP tests used to calculate that domain. Therefore, I chose to include those tests, where available, in the global measure of cognition but did not analyze processing speed as an independent cognitive domain.

While some participants in this cohort had up to 13 NP examinations, the decrease in the number of people undergoing NP examinations after 6 exams was high. For the purpose of this analysis and ability to appropriately fit the LGCM models, I limited the study and analyzed trajectories up to and including 6 exams, a cut point at which less than 10% of the cohort had available NP data (Appendix Table A.2).

Sociodemographic Risk Factors. At enrollment, participants underwent in-person interviews in their primary language (English or Spanish) conducted by trained interviewers to assess sociodemographic characteristics, baseline health status and risk factors using validated data collection instruments, physical, and neurological examinations. Race-ethnicity was collected through self-identification using the format of the 2000 US Census. All individuals were first asked to report their racial group and then, in a second question, were asked whether they were of Hispanic origin. For the purpose of analysis, individuals were characterized into White non-Hispanic, Black non-Hispanic, Hispanic, and other. Education was collected through self-report as total years of education completed. A summary z-score for socioeconomic status (SES) was derived at the census tract level as a neighborhood measure of wealth, education, and occupation (238).

Data Analysis

Distributions of sociodemographic characteristics and exposure measures were calculated as means for continuous variables and proportions for categorical variables. A series of conditioned latent growth curve models (LGCM) were then used to examine the baseline levels of cognitive function (intercept; I), and the average rate at which individual participants' trajectories change over time (slope; S) (239,240).

I first ran a series of unconditional LGCM models (Model 0) for each of the four outcomes of interest (global cognition, executive function, memory, and language) in which I assessed the influence of varying fixed and random effects, and linear and quadratic trends over time. The selection of the best model was based on the Schwartz Bayesian information criterion (BIC), with lower values indicating better fit. Upon identifying the best base model fit, I then allowed for up to three latent trajectory classes. Accuracy of classification into distinct trajectory classes was assessed using entropy values ranging from 0 to 1, with values closer to 1 corresponding to better classification accuracy. I assessed individual model fit using the following indices: Chi-square (x^2); comparative fit index (CFI), Tucker Lewis Index (TLI); Root Mean Square Error of Approximation (RMSEA) with 90% confidence intervals; and the Standardized Root Mean Residual (SRMR). Based on prior studies, I used CFI and TLI values greater than 0.90 and RMSEA values less than 0.08, and an non-significant Chi-square value to identify an appropriately fit model (241).

After comparing models I identified the best fit model to be one that allowed for random effects of both the intercept and slope, and included a quadratic term for time (Appendix Table A.3). Increasing the number of trajectory classes decreased the BIC, but upon applying a restriction that there must be at least 5% of participants in a class to be meaningful clinically and numerically stable (242), I chose a one-class model as the best fit. Overall, model fit statistics of the unconditional LGCM for each outcome were acceptable. The Chi-square value was significant for each, indicating an inappropriate model fit, however, the significance of the Chi-square test is very sensitive to sample size with small differences found to be significant in large samples (243). In contrast, other fit indices suggested a well fit model (Appendix Table A.4).

To examine the crude effect of long-term ambient air pollution on baseline cognition and subsequent trajectories of change, the intercept and slope parameters identified for each outcome through Model 0 was regressed on each of the three measures measure of air pollution ($PM_{2.5}$, PM_{10}, NO_2, and distance to roadway) in separate models (Model 1). Individual socio-demographic characteristics were adjusted for in Model 2, including sex, age at baseline examination, race-ethnicity, and education (135,244). Model 3 adjusted for neighborhood level SES using a census-based summary z-score (238). An example path diagram for the fully adjusted LGCM for global cognitive decline is shown in Appendix Figure A.2. Covariates were included in the models as potentially influencing both the intercept and the slope. All analyses were conducted using the full maximum likelihood method in order to appropriately handle missing data (245) and reported as standardized (STDXY) effects due to continuous nature of both the exposures and outcomes.

All data cleaning and descriptive analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC) Latent growth curve analyses were performed using Mplus Version 8 (Muthen & Muthen, Los Angeles, California) (246,247).

RESULTS

Cohort characteristics are outlined in Table 2.2. Median age (standard deviation; SD) at time of baseline NP examination was 74.8 ($\pm$9.67) years. The cohort was predominately women (66%). Approximately half of the cohort identified as Hispanic (47%), 28% as non-Hispanic Black, and 23% as non-Hispanic White. On average, participants had 9.5 years of education (SD $\pm$ 4.9). Mean [IQR] annual exposure estimates to ambient air pollution were 13.2 [4.5] $\mu g/m^3$ for $PM_{2.5}$, 20.2 [9.6] $\mu g/m^3$ PM_{10}, and 31.7 [10.7] ppb NO_2; participants lived an average 303 meters from a major roadway.

The unconditional LGCM (Model 0) indicated a slight decrease in mean global cognitive score over time ($S_{global} = -0.410$, p = <0.001, Figure 2.1). Overall, exposure to higher levels of ambient air pollution was highly predictive of cognitive domain scores, but at baseline only. Table 2.3 presents parameter estimates for the intercepts and slopes for global cognition and each of the three functional domains (additional data found in Appendix Tables A.5-A.8). The intercept value (I) is interpreted as the mean cognitive score at baseline while the slope (S) is the predicted increase in cognitive score per one IQR increase in exposure. Adjustment for individual level sociodemographic variables attenuated the estimates only slightly; in fully conditioned models (Model 3), a one IQR increase in $PM_{2.5}$ was predictive of a 0.16 unit lower global cognitive score at baseline ($I_{global} = -0.16$ $p<0.001$). Similarly, a one IQR increase in PM_{10} and NO_2 was predictive of a 0.13 and 0.16-unit lower baseline global cognitive score, respectively (PM_{10} I_{global} = -0.125 $p<0.001$; NO2 I_{global} = -0.159 p=0.01).

I found no evidence of an association between particulate matter and change in global cognitive scores over time ($PM_{2.5}$ S_{global} = -0.505, p=0.22; PM_{10} S_{global} = -0.059 p=0.09). A one IQR increase in NO_2, however, was predictive of statistically significant steeper rates of global cognitive decline score (standardized S_{global}= -0.08, p=0.04).

Results from the three individual functional cognitive domains were similar. Mean cognitive domain scores decreased over time in unconditioned models (Model 0, Figure 2.1). Overall, a one IQR increase in $PM_{2.5}$, PM_{10}, and NO_2 was significantly associated with lower baseline cognitive scores in each of the three domains (Table 2.3, additional data in Appendix Tables A.9-A.21). There was no association with pollutant measures and individual functional cognitive change over time.

Residential distance to roadway was not strongly associated with either baseline cognitive scores or change in cognition over time (Table 2.3). A statistically significant effect was seen in both the global cognitive score and language domains at baseline, although the magnitude of effect was very small (I_{global}= -.009; Standardized $I_{language}$=-0.033, all p<0.01). Distance to roadway was not associated with longitudinal change in cognitive scores.

Sensitivity Analyses. I ran a series of sensitivity analyses in an attempt to ascertain and quantify bias at several points throughout the study. A key limitation in the analysis of longitudinal cohort studies is subject ascertainment and the impact of subject dropout and death. I have attempted to address this in several ways. A benefit of using LGCM models to assess trajectories of decline is that there is no need to remove individuals with only one NP Examination as they will still contribute to the calculation of the latent intercept. However, there are likely reasons that individuals drop out of a study early that are related to the outcome, particularly for cognitive dysfunction and dementia. If these individuals are only contributing to the intercept, they may bias the analyses. I addressed this by performing a sensitivity analysis including only those with 2 or more NP examinations. Results of these models were not substantially different from those in the full cohort (Appendix Table A.22). I next re-ran all models excluding all participants who had died prior to undergoing 6 NP examinations in an attempt to mitigate death as a competing risk. Air pollution is a known cause of death and therefore could be increasing the risk of death in this population before any cognitive symptoms begin to manifest. Despite 38% of participants dying before completion of the study, limitation of the population did not change the overall results of the analyses (Appendix Table A.23). Another area for potential bias in this analysis was misclassification of exposure due to individuals moving throughout the study period. Some studies have tried to mitigate this bias by including only those participants identified as either movers or non-movers. In this study, I found that a substantial percentage of the combined cohort (58%) did not have available baseline residential data (Waves II and III of the WHICAP Study), and therefore could not be identified as 'non-movers'. In individuals with complete baseline data, I found that 91% of them did not move throughout the study period. The LGCMs on the sample of non-movers with available data did not converge and therefore could not be compared to the results of the full cohort. Given that the sampling of the cohort did not change over time, there is no reason to believe that individuals with complete residential data are substantially different than those without and so it can be expected that there is limited residential mobility in those individuals as well. In addition, any measurement error arising from those individuals moving throughout the study period is expected to be non-differential and therefore bias the effects of the analysis towards the null.

DISCUSSION

In this urban, population based cohort in Northern Manhattan, I found evidence of an adverse effect of ambient air pollution on the baseline cognitive functioning of older adults. While limited evidence was found between air pollution and trajectories of cognitive decline, I did find a significant association between increased levels of NO_2 and steeper trajectories of decline. These findings are consistent with previous research linking air pollution to cognition in older adults (114,144,148,150,151,154,155,160,164–181). This study, however, is the largest to have studied cognitive decline over time in a racially and ethnically diverse sample to date.

In this study, I found that within each cognitive domain, the magnitude of effect was relatively consistent when comparing results from each of the three pollutant measures. The strongest magnitudes of effect were seen in the executive function domain, with a one IQR increase in pollutant level associated with a 0.17 to 0.23 unit lower executive function score at baseline. The similarity across pollutant estimates is likely due to the fact that these pollutants don't exist in isolation and these analyses are likely measuring the effect a mixture of these pollutants are having on cognition and cognitive decline. Further studies should attempt to differentiate the individual effects of each pollutant. In all analyses, residential distance to roadway had smaller, non-significant measures of effect. This may have been due to limited variability of the exposure measure, or that in this cohort, it is a non-specific measure of air pollution.

In this cohort, the effects of air pollution on cognition were found on cognitive levels at baseline but only NO_2 showed an association with cognitive decline. A limitation of this study is that many of the physiological processes preceding cognitive decline have been found to begin much earlier in life, and risk factors at midlife have been shown to be more important for process of accelerated cognitive decline (1,26,27,31,33). These results are consistent with this theory, having shown that pollutant levels at later life do not have a significant impact on cognitive decline, but may be influencing levels of cognition earlier in life by being associated with only cognition at baseline. Assessing midlife risk factors is not possible in these two cohorts, but the results from the proposed study can be used to inform future studies which better look at a life course approach of environmental effects on cognitive aging.

There is growing concern regarding the deleterious health effects of ambient air pollution and several biological mechanisms have been proposed to explain mechanisms behind the adverse effects on the brain and cerebral vasculature. A series of experimental animal studies indicate that ambient particles may impact the central nervous system either through a systemic response via the circulatory system, or intra-nasally by direct translocation to the brain through the olfactory bulb (50,211,212). Once inside pollutant particles activate a series of systemic inflammatory pathways leading to vascular inflammation (203,216,217), impaired microvascular reactivity (218), and changes in cerebral hemodynamics (219). Further evidence of these mechanisms comes from a series of studies done in Mexico City where strong histological evidence of cerebral microvascular damage, systemic inflammatory markers, and brain pathology has been observed in autopsied brains of dogs and children residing in high versus low pollutant areas (220,222).

Overall, the results for the effects of air pollution and cognitive function were strongest in the executive function domain. Loss of executive function is a symptom of vascular dementia, a sub-type of dementia with key risk factors that include stroke, diabetes, high blood pressure, and heart attack. Exposure to high levels of air pollution have also been linked to an increased risk of these same factors (63,95,96,105,106,228), therefore it is quite possible that these are actually acting as mediators along this pathway. While knowledge behind the mechanisms of impact between air pollution and cognition are still limited, these findings fit in with the current research linking air pollution to cognition and other cardiovascular diseases. Future studies should begin to examine these mechanisms.

Limitations and Strengths. The current study adds to the growing scientific evidence supporting the importance of exposure to air pollution in aging brain health, although this analysis had several important limitations. In an urban study area with limited geographic extent such as Northern Manhattan, there may have been limited spatial variability in exposure levels. As compared to previously studies performed only with the NOMAS cohort the combined cohort used had wider spatial variability in exposure measures (135,248). In addition, the urban study area is strength of this study since this is one of the few studies to focus primarily on intra-urban variation in measures of ambient air pollution, eliminating many potential unmeasurable confounders that may have existed in prior studies which compare participants living in different urban and/or rural areas. In addition, although I adjusted for individual-level measures of SES in our analysis (education, race-ethnicity), I was unable to adjust for individual income levels. I included a validated census derived SES z-score to adjust further for variations in neighborhood level SES throughout the study area.

Another limitation is that the estimates of air pollution are indirect, based on spatiotemporal modeling from monitors located throughout Northern Manhattan, a method that could potentially lead to biased results (194). The MESA-Air estimates are well validated, however, and positive associations with other health outcomes such as blood pressure, atherosclerosis, and cardiovascular disease have been identified using this model (127,249). Measurement error would likely be non-differential; attenuating our estimates, therefore the effects of air pollution found here would likely be true.

In addition, the pollution estimates do not include data on time spent in locations outside the home. Because of the older age of our participants, a high percentage of them were retired at the time of the study, and there is limited data on lifetime workplace pollution exposures. Occupational exposures seem unlikely to be associated with residential outdoor levels of air pollutants. In addition, the measurement of late-life environmental exposures does not necessarily indicate an individual's true lifetime exposure. Levels of traffic-related air pollutants have decreased by almost 70% in the United States since the implementation of the Clean Air Act in 1970 (49), therefore individuals may have been exposed to much higher levels of pollution throughout their lives as compared as to what was measured for the purpose of this study.

However, the use of MESA-Air methods allowed the assignment of pollution exposure levels to participants' addresses over time using geocoded coordinates, increasing the accuracy of the estimates and reducing potential easurement bias. In prior studies and in this dissertation analysis, I have attempted to mitigate any bias due to methodological difficulties in defining and estimating long-term measures of exposure to air pollution by categorizing pollution in multiple ways, and measuring several different components. I also performed sensitivity analyses to attempt to quantify any bias brought on by limiting the analytical sample to those individuals who had not moved over the study period. While the LGCM models did not converge in the sensitivity analysis, descriptive analyses found that individuals considered ‘movers’ were slightly younger and more likely to be male and of Hispanic ethnicity. There were limited differences between levels of ambient air pollution across groups.

A key limitation of this dissertation study is that longitudinal measures of cognition were measured at different time points and with different numbers of available across individuals in each of the two cohorts. I have chosen to use latent growth curve models to address this limitation. LGCM can more robustly handle this type of data and has several strengths over traditional mixed effect models (246,247,250,251). In general, LGCMs are more flexible and can more robustly handle missing data and unequally spaced time points. In addition, the use of growth curve models allows for the inclusion of all available data points without the need to perform a complete case analysis, potentially mitigating some of the selection bias towards more cognitively healthy individuals.

A limitation inherent in longitudinal studies of cognition may have also influenced the results of this analysis (252). Practice effects, or improvements in NP test performance due to repeated examinations, may also have been a source of error in this analysis. However, because these effects are not likely to be influenced by pollutant measures, any bias caused by these effects would be biased towards the null.

The NOMAS and WHICAP cohorts included in this proposal provided a unique opportunity to evaluate multi-dimensional data in a population of over 6,000 residents of Northern Manhattan and there are several key strengths to this study. Combining two large, prospective cohorts, NOMAS and WHICAP, has led to the largest longitudinal analyses of ambient air pollution and cognitive decline to date, with over 6,000 participants included in the analysis. In addition, the use of these two cohorts has several benefits over many of the current studies.

Earlier studies have shown that prevalence of cognitive decline and dementia vary by sex and race-ethnic group; the prevalence of cognitive decline and dementia is higher in women (185,186) and non-Hispanic whites (187–193), while older African Americans are twice as likely and Hispanics are 1.5 times as likely as older non-Hispanic whites to develop incident dementia. (187–193) It is important to have a racially and ethnically diverse population of older adults that are not limited by sex to be able to ascertain differences in higher risk groups and also be able to generalize results to an aging urban population. Another benefit of this large combined cohort was the ability to analyze trajectories of cognitive decline over time using well validated NP tests, a key limitation of many of the current cross-sectional studies of air pollution and cognition.

A second strength to the current study was the use of individual-level estimates of several different components of air pollution in order to get a full picture of the influence of air pollution on the cognitive health of an aging urban population. A final strength to the proposed dissertation is the series of sensitivity analyses that have been proposed to both identify and quantify bias in several areas throughout the study.

In conclusion, as global life expectancy continues to increase, the rates of age-related cognitive decline and dementia are expected to skyrocket. To date, there is no current consensus on key modifiable risk factors are for cognitive decline; therefore, the identification of novel risk factors is of great importance. This study found that individuals exposed to higher levels of ambient air pollutants have lower cognition scores at baseline, with limited evidence that presence of these pollutants caused individuals to decline more rapidly over time. These results support the current evidence on the role of air pollution on accelerated cognitive aging and brain health.

TABLES AND FIGURES

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<tr><th colspan="4">Table 2.1 Neuropsychological Test Batteries in the Northern Manhattan Study (NOMAS) and the Washington Heights Inwood Community Aging Project (WHICAP)</th></tr>
<tr><th colspan="2">Cognitive Function Domain</th><th>NOMAS</th><th>WHICAP</th></tr>
<tr><td rowspan="7">Global Cognition Score</td><td>Memory</td><td>Modified California Verbal Learning Test (CVLT) (253)</td><td>Selective Reminding Test</td></tr>
<tr><td rowspan="2">Executive Function</td><td colspan="2">(Color Trails 2 (254,255) - Color Trails 1 (256)), COWAT</td></tr>
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<tr><td>Grooved Pegboard (260,261), Letter Number Sequencing (262), Symbol Digit Modalities (263)</td><td></td></tr>
</table>

Table 2.2 Characteristics of the Combined Northern Manhattan Cohort (n=6,206)	
Sociodemographic Characteristics	**Mean [SD] or n (%)**
Age at baseline, y	74.8 [9.67]
Men	2097 (33.8)
Race-ethnicity	
White non-Hispanic	1426 (23.0)
Black non-Hispanic	1749 (28.2)
Hispanic	2936 (47.3)
Other	95 (1.50)
Years of Education	9.49 [4.90]
Census Z-Score	-2.92 [3.58]
Cardiovascular Risk Factors	
Smoking Status	
Current or Former	2,690 (46.5)
Never	3,495 (56.5)
Hypertension†	4761 (76.7)
Diabetes‡	1,696 (27.2)
Any Cardiac Disease	2,144 (34.6)
Pollutant Exposures	**Mean [IQR] or n(%)**
$PM_{2.5}$ ($\mu g/m^3$)	13.2 [4.46]
PM_{10} ($\mu g/m^3$)	20.2 [9.63]
NO_2 (ppb)	31.7 [10.7]
Continuous Residential Distance to Roadway (m)	303.1 [276.7]

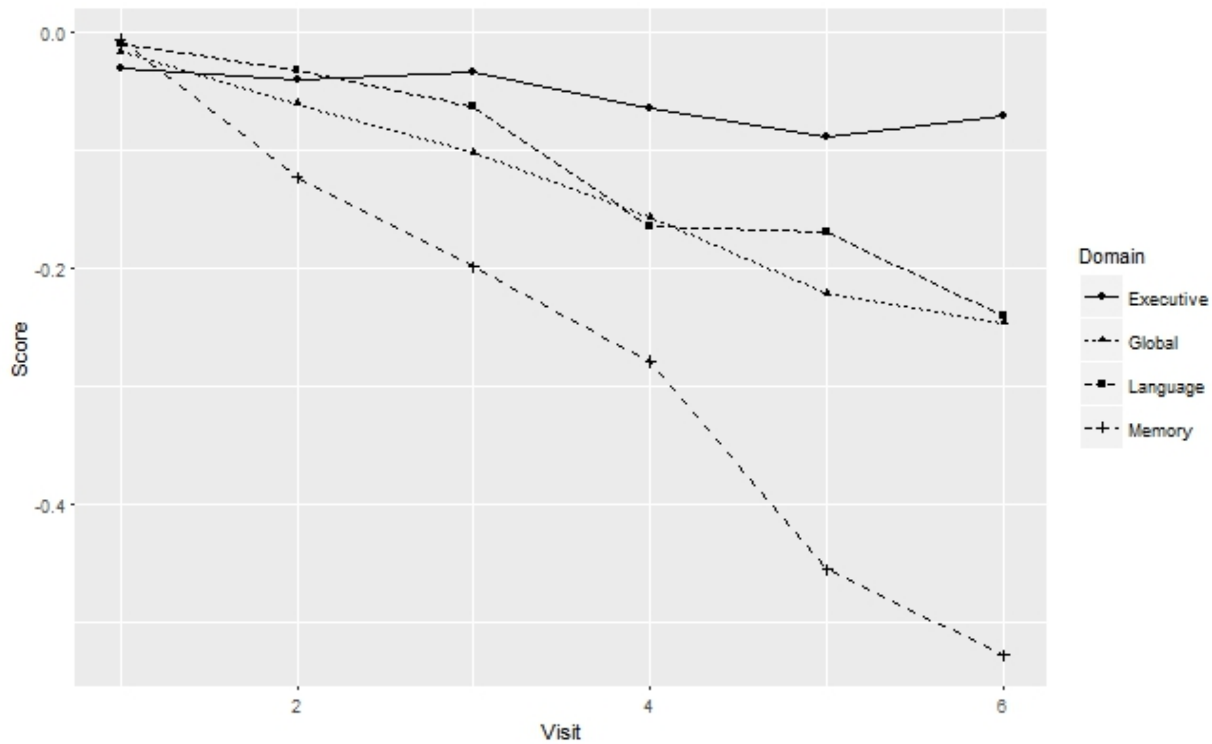
IQR indicates interquartile range.
†Hypertension = systolic blood pressure > 140 mm/Hg, diastolic blood pressure recording >90 mm/Hg (based on the average of two measurements), physician diagnosis, or self-report, ‡Diabetes=fasting blood glucose ≥ 126 mg/dL, self-report, insulin, or hypoglycemic use

Table 2.3 Parameter Estimates of Conditioned Latent Growth Curve Models for the Association between Ambient Air Pollution and Cognition						
	Model 1		**Model 2**		**Model 3**	
	Estimate (SE)	p-value	Estimate (SE)	p-value	Estimate (SE)	p-value
Global Cognitive Score						
PM2.5						
→ I_{global}	-0.18 (0.01)	<0.01	-0.17 (0.01)	<0.01	-0.16 (0.01)	<0.01
→ S_{global}	-0.07 (0.04)	0.08	-0.05 (0.04)	0.25	-0.05 (0.04)	0.22
PM_{10}						
→ I_{global}	-0.16 (0.02)	<0.01	-0.14 (0.01)	<0.01	-0.13 (0.014)	<0.01
→ S_{global}	-0.12 (0.04)	<0.01	-0.06 (0.04)	0.11	-0.06 (0.035)	0.09
NO_2						
→ I_{global}	-0.23 (0.01)	<0.01	-0.18 (0.01)	<0.01	-0.16 (0.01)	<0.01
→ S_{global}	-0.13 (0.04)	0.01	-0.07 (0.04)	0.06	-0.08 (0.04)	0.04
Residential Distance to Roadway						
→ I_{global}	0.06 (0.01)	<0.01	-0.01 (0.01)	0.35	-0.01 (0.01)	0.44
→ S_{global}	0.001 (0.03)	0.98	-0.001 (0.03)	0.98	-0.002 (0.03)	0.94
Memory Domain						
$PM_{2.5}$						
→ I_{mem}	-0.15 (0.01)	<0.01	-0.13 (0.01)	<0.01	-0.11 (0.01)	<0.01
→ S_{mem}	-0.08 (0.04)	0.06	-0.06 (0.04)	0.17	-0.05 (0.04)	0.19
PM_{10}						
→ I_{mem}	-0.11 (0.01)	<0.01	-0.06 (0.01)	<0.01	-0.05 (0.01)	<0.01
→ S_{mem}	0.02 (0.03)	0.56	0.08 (0.03)	0.02	0.08 (0.03)	0.02
NO_2						
→ I_{mem}	-0.17 (0.01)	<0.01	-0.11 (0.01)	<0.01	-0.88 (0.01)	<0.01
→ S_{mem}	-0.03 (0.04)	0.42	0.02 (0.04)	0.58	0.03 (0.04)	0.47
Residential Distance to Roadway						
→ I_{mem}	0.05 (0.01)	<0.01	0.002 (0.01)	0.85	0.004 (0.01)	0.74
→ S_{mem}	-0.02 (0.03)	0.53	-0.02 (0.03)	0.45	-0.02 (0.03)	0.40
Executive Function Domain						
$PM_{2.5}$						
→ I_{exec}	-0.24 (0.01)	<0.01	-0.25 (0.01)	<0.01	-0.23 (0.01)	<0.01
→ S_{exec}	0.27 (0.13)	0.04	0.38 (0.16)	0.02	0.34 (0.14)	0.02
PM_{10}						

→ I_{exec}	-0.18 (0.02)	<0.01	-0.19 (0.01)	<0.01	-0.17 (0.01)	<0.01
→ S_{exec}	-0.05 (0.07)	0.49	0.09 (0.07)	0.24	0.07 (0.07)	0.32
NO_2						
→ I_{exec}	-0.29 (0.02)	<0.01	-0.25 (0.01)	<0.01	-0.23 (0.01)	<0.01
→ S_{exec}	0.05 (0.08)	0.74	0.19 (0.10)	0.05	0.13 (0.09)	0.14
Residential Distance to Roadway						
→ I_{exec}	0.07 (0.02)	<0.01	-0.01 (0.01)	0.57	-0.01 (0.01)	0.68
→ S_{exec}	0.09 (0.06)	<0.01	0.07 (0.06)	0.27	0.07 (0.06)	0.26
Language Domain						
$PM_{2.5}$						
→ I_{lang}	-0.17 (0.01)	<0.01	-0.17 (0.01)	<0.01	-0.14 (0.01)	<0.01
→ S_{lang}	-0.08 (0.05)	0.10	-0.05 (0.05)	0.28	-0.07 (0.05)	0.18
PM_{10}						
→ I_{lang}	-0.19 (0.01)	<0.01	-0.18 (0.012)	<0.001	-0.16 (0.01)	<0.01
→ S_{lang}	0.14 (0.04)	<0.01	0.19 (0.041)	<0.001	0.18 (0.04)	<0.01
NO_2						
→ I_{lang}	-0.25 (0.02)	<0.01	-0.20 (0.01)	<0.01	-0.16 (0.01)	<0.01
→ S_{lang}	0.14 (0.04)	0.76	0.06 (0.04)	0.19	0.04 (0.05)	0.32
Residential Distance to Roadway						
→ I_{lang}	0.03 (0.01)	0.03	-0.28 (0.01)	0.02	-0.03 (0.01)	<0.01
→ S_{lang}	0.03 (0.03)	0.38	0.03 (0.03)	0.34	0.03 (0.03)	0.37

Model 1: crude model
Model 2: Adjusted for individual sociodemographic variables (age, education, sex, race/ethnicity)
Model 3: Adjusted for individual and neighborhood sociodemographic variables (Model 2 + Census based SES z-score)

Figure 2.1 Mean cognitive scores over time.



CHAPTER THREE.

Effect Modification of the Association between Long-term Exposure to Ambient Air Pollution and Cognitive Decline in a Population-based cohort in Northern Manhattan

INTRODUCTION

Air pollution, a largely ubiquitous environmental exposure, is rapidly becoming a widespread public health hazard, particularly in urban areas. Despite significant decreases in overall levels of ambient air pollution over the last decade, levels remain high. As of 2011, 124 million United States residents were living in areas that did not meet the US Environmental Protection Agency (EPA) National Ambient Air Quality Standards (49).

Studies have suggested older adults are particularly vulnerable to the health effects of adverse environmental exposures, which can cause amplified respiratory and cardiovascular symptoms, exacerbations of existing diseases, and increased mortality (55–57). Long-term exposure to pollution has been associated with increased risk of incident cardiovascular disease (CVD) (95,96,105), acute myocardial infarction (MI) (228), heart failure (63,106), and death (97,114–118,120,121), with several large cohort studies highlighting the association between fine particulate matter exposure and overall CVD mortality (67,97–103). The evidence linking air pollution with the cardiovascular and cerebrovascular systems suggest it may also have a damaging impact on the brain and cognitive processes. Long-term exposure to air pollution has recently been highlighted as a risk factor for cognitive decline (149,154,166,170,173,175). Age-related cognitive decline is a growing public health concern; an estimated 46.8 million individuals are currently living with dementia, with the global prevalence expected to double every 20 years (1). In addition, poor cognitive function is a key cause of disability among older adults and can have profound social, economic, and health implications (139,227).

The mechanisms behind this association between ambient air pollution and cognition are largely unknown, however it has been suggested that several behavioral and clinical risk factors may modify this association. Age is considered a significant risk factor for cognitive decline and also a potential modifier. A study by Ranft et al. found that living 5-m from a high traffic road was associated with lower CERAD-plus scores only in women <74 years old, with no association in those older than 74 years old (179). Tzivian et al. found that depression was also a significant effect modifier, with those considered depressed having higher rates of a mild cognitive impairment (MCI) diagnosis (172). Within the Health and Retirement Study, interactions were tested between a sizeable list of sociodemographic characteristics and cardiovascular risk factors, finding that the only significant effect modifier was smoking (174). In other studies, tests for interaction between cardiovascular risk factors (166,180), and the apolipoprotein E ε4 (APOE-ε4) allele (164) resulted in non-significant associations. Despite these findings, evidence for potential effect modification of the relationship between air pollution and cognition remains limited.

Previous work done in a combined cohort in Northern Manhattan demonstrated an association between long-term exposure to ambient air pollution and cognitive function in an elderly urban population (Chapter 2). Herein, I expand on previous analyses by testing the hypothesis that both genetic and behavioral risk factors have an association with cognition and are able to modify the air pollution-cognition relationship. I examined two previously tested modifiers, age and smoking status among older adults in an urban population within Northern Manhattan. In a subset of study participants with available genetic data, I also examined whether the presence of heterogeneous APOE-ε4 alleles modified this association.

METHODS

Data collection

I have brought together two prospective, population-based cohorts, the Northern Manhattan Study (NOMAS) and the Washington Heights Inwood Community Aging Project (WHICAP) to study the association between exposure to ambient air pollution and age-related cognitive decline.

The Northern Manhattan Study (NOMAS). NOMAS is an ongoing, prospective, population-based cohort study designed to measure cardiovascular risk factors and outcomes in a stroke-free multi-ethnic urban population in Northern Manhattan. Cohort recruitment occurred from 1993 to 2001 and participants are followed-up annually be telephone. Initial edibility included those aged $\geq$ 40 years, permanent residency of one of Northern Manhattan's 5 zip codes, lived in a house with a telephone, and no history of clinical stroke. Detailed methods of participant recruitment and follow-up have been described previously (229,230). NOMAS participants, and eligible household members, were recruited during annual follow-up to participate in a MRI sub-cohort if they met the following eligibility criteria: free of clinical stroke, free of clinically identified dementia, aged ≥50 years, and had no contraindications to MRI. Those participating in the MRI (n=1,290) cohort underwent a standardized medical exam, MRI, and detailed neuropsychological (NP) exam at time of enrollment. Follow-up NP testing at a 5-year interval was completed on approximately 85% (n=989) of the surviving MRI cohort and evaluated for changes in risk factors, medication, and cerebrovascular events on an annual basis.

The Washington Heights Inwood Community Aging Project (WHICAP). WHICAP was established in three recruitment waves: 1992 (n=2234), 1999 (n=2180), and 2010 (n=2125). Detailed sampling strategies and recruitment outcomes have been discussed previously (231,232). The first wave of participants was recruited in 1992 from a random sample of Medicare-eligible adults (age ≥65) residing in the neighborhoods of Washington-Hamilton Heights and Inwood in Northern Manhattan representing three broadly defined racial/ethnic categories (i.e., Caribbean Hispanic, black, non-Hispanic white). The second and third cohorts were recruited from the same community. These cohorts were not randomly identified, but chosen based on the following criteria: (1) the sample would be equally divided among Hispanics, non-Hispanic blacks, and non-Hispanic whites, (2) the cohort would represent equal proportions of 65-74 and ≥ 75 year olds, and (3) individuals would be excluded if they had significant cognitive problems or had been diagnosed with having dementia. To date, at least one NP battery has been collected on 6,261 older adults, of which 13% had signs of dementia at baseline, leaving a final sample size of 5,478 non-demented individuals. Participants are evaluated longitudinally every 18-24 months, with a comprehensive NP battery, medical and neurological examination, and survey about lifestyle factors, medication, comorbidities, and risk factors.

Combination of Prospective Cohorts. A single analytical cohort was created by combining the NOMAS and WHICAP populations into a single prospective analytical cohort. The source populations from both studies were similar, and cohorts were recruited from overlapping neighborhoods in Manhattan, therefore I first set out to identify individuals who were participating in both cohorts. To do this, I matched individuals across the two cohorts using a combination of identifying features. Individuals were matched on four identifying characteristics: date of birth, sex, name, and race/ethnicity. Individuals who matched on all four characteristics were automatically linked and identified as being in both cohorts; those with 2 or 3 matching factors were hand matched to identify overlap. Individuals with less than 2 matching factors were automatically considered to be non-overlapping. In all, there were 240 individuals that were participants in both cohorts. All available cognitive assessments were used for the overlapping individuals.

The final analytical sample was comprised of individuals from both cohorts that were: (1) free of dementia at baseline, (2) have at least one NP examination at any point during the study period, (3) had primary addresses in NYC at time of baseline NP Examination due to availability of air pollution exposure models, (4) did not having missing data for any of the exposure or confounding variables, and (5) had enough non-missing NP data to calculate a global cognitive score. These exclusion criteria resulted in a total sample size of 6,206 individuals. A random sub-sample of individuals across both cohorts had received genotyping; all analyses of APOE-ε4 allele will be performed in the sample of 4,594 individuals with available data (Appendix Figure A.1).

All activities pertaining to NOMAS and WHICAP were approved by the Institutional Review Board at Columbia University Medical Center. Written consent was provided by each participant at enrollment.

Assessment of Ambient Air Pollution. Participants' residential addresses were collected at each longitudinal follow-up and when available, address histories were reconstructed for baseline and at each NP assessment. Participants were classified as 'non-movers' if they were identified as not having moved throughout the study period, and 'movers' if they had different addresses at baseline and time of last NP Exam. In this combined cohort, 90.6% of participants with available data were non-movers (n=2,339). 3,625 of all participants (58%) had only one available address due to data collection procedures and could not be categorized into 'movers' vs. 'non-movers'.

Primary analyses used all individuals in both cohorts, and sensitivity analyses were performed by limiting analyses to non-movers only in order to ascertain the potential for measurement error due to changing residential locations. Residential addresses were geocoded using Geosupport Batch Address Translator Desktop Edition (NYC Department of City Planning, NY, NY). Only participants with primary addresses in New York City at the time of last NP exam were included in the analysis due to availability of air pollution exposure models.

Prior research in the NOMAS cohort identified the average pollutant level for 1 year to be a valid marker of long-term pollution (135), so estimates of residential air pollution exposure one year prior to baseline NP were ascertained using models developed for Multi-Ethnic Study of Atherosclerosis and Air Pollution Study (MESA-Air), as previously described (233–236). Ambient concentrations of fine particulate matter less than 2.5 μm in diameter ($PM_{2.5}$; μg/m^3), coarse particulate matter (PM_{10}; μg/m^3), and nitrogen dioxide (NO_2; ppb) were estimated for each address. MESA-Air pollution models utilized monitoring data from the U.S. EPA Air Quality System, monitors placed by MESA-Air at sites throughout the New York City area, and at MESA participants' homes. In addition, models included geographic covariates (roadway density, population density, urban land, agricultural land, forests, bodies of water), and outputs from dispersion models to improve predictions. These models permit characterization of seasonal time trends, key sources of spatial variability within study area, and underlying spatial and spatiotemporal correlation. All exposures were obtained and analyzed as continuous variables and included in models per inter-quartile range (IQR).

Distance from participant residence to the nearest major roadway was calculated as a secondary marker of long-term exposure to traffic pollution. ArcGIS (version 10.3.1, ESRI, Inc., Redlands CA) was used to calculate the Euclidean distance from geocoded residence to nearest major roadway, defined as US Census Features Class A1 (primary highway with limited access) or A2 roadway (nationally and regionally important highways that do not have limited access), which include most federal and interstate highways and some larger state and county highways. Residential distance to roadway was modeled as a log-transformed continuous variable (per interquartile range (IQR)) based on prior studies (90,135).

Outcome Ascertainment. NP batteries used in NOMAS and WHICAP were very similar; both were designed to capture key cognitive domains in both English and Spanish speaking older adults and developed to permit the calculation of domain-specific z-scores that allow for efficient cross-cohort harmonization for combined analysis due to a large number of overlapping tests (Table 3.1). Cognitive decline was measured in two ways: (1) trajectories of change in global cognition scores and (2) trajectories of performance in individual cognitive domains.

In order to utilize all available NP data for each cohort, available tests were harmonized across the two studies as previously described (see Appendix, Chapter 2). Briefly, all NP tests were standardized into z-scores using combined cohort-specific means and standard deviations at baseline. A confirmatory factor analysis (CFA) was used to confirm data fit into previously identified four factor structures. Weights were calculated from the factor scores of the final CFAs (Appendix Table A.1). A global cognition score was constructed using the weighted mean of the z-scores of all NP Tests used to calculate the functional domains and was used as the primary outcome. Secondary outcomes were measured as performance in Memory, Executive Function, and Language functional domains and were expressed as the weighted mean of the individual test z-scores loading into each domain. When analyzing the processing speed domain the adjusted models did not converge, due to a large amount of missing data in the NP tests used to calculate that domain. Therefore, I chose to include those tests, where available, in the global measure of cognition but did not analyze processing speed as an independent cognitive domain.

While some participants in this cohort had up to 13 NP examinations due to loss of follow-up as the studies progressed, I used data up to and including six NP examinations (Appendix Table A.2).

Sociodemographic Risk Factors. At enrollment, participants underwent in-person interviews in their primary language (English or Spanish) conducted by trained interviewers to assess sociodemographic characteristics, baseline health status and risk factors using validated data collection instruments, physical, and neurological examinations. Race-ethnicity was collected through self-identification using the format of the 2000 US Census. All individuals were first asked to report their racial group and then, in a second question, were asked whether they were of Hispanic origin. For the purpose of analysis, individuals were characterized into White non-Hispanic, Black non-Hispanic, Hispanic, and other. Education was collected through self-report as total years of education completed. A summary z-score for socioeconomic status (SES) was derived at the census tract level as a neighborhood measure of wealth, education, and occupation (238). For the purpose of assessing effect modification, age was categorized into < 75 years versus ≥ 75 years old based on the mean age of the cohort. Smoking status obtained through self-report and dichotomized into never smokers versus former or current smokers for analysis. APOE genotypes were dichotomized based on the number of APOE-ε4 alleles. Individuals with at least one copy of the APOE-ε4 allele were considered to be exposed to the modifier, as done in prior studies (264,265). Blood samples taken from each individual at any point in the study were utilized, and the pattern of each individual's APOE-ε4 isoforms was identified similarly across the two cohorts using the method of Hixson and Vernier (266).

Data Analysis

Distributions of sociodemographic characteristics and exposure measures were calculated as means for continuous variables and proportions for categorical variables. A series of conditioned latent growth curve models (LGCM) were then used to examine the baseline levels of cognitive function (intercept; I) and the average rate at which individual participants' trajectories change over time (slope; S) (239,240).

A series of unconditional LGCM models (Model 0) were run for each of the four outcomes of interest (global cognition, executive function, memory, and language) in which I assessed the influence of varying fixed and random effects, and linear and quadratic trends over time (See Appendix for detailed model fit methods). Briefly, selection of the best model was based on Schwartz Bayesian information criterion (BIC), with lower values indicating better fit (Appendix Table A.3). After comparing models I identified the best fit model to be a one-class model that allowed for random effects of both the intercept and slope and included a quadratic term for time (Appendix Table A.4). Based on prior studies, I used comparative fit index (CFI) and Tucker Lewis Index (TLI) values greater than 0.90 and Root Mean Square Error of Approximation (RMSEA) values less than 0.08, and an insignificant chi-square value to identify appropriate fit in conditioned models (241).

To examine the crude effect of long-term ambient air pollution on baseline cognition and subsequent trajectories of change, the intercept and slope parameters identified for each outcome through Model 0 was regressed on each of the three measures measure of air pollution ($PM_{2.5}$,

PM_{10}, NO_2, and distance to roadway) in separate models (Model 1). Individual socio-demographic characteristics were adjusted for in Model 2, including sex, age at baseline examination, race-ethnicity, and education (135,244). Model 3 adjusted for neighborhood level SES using a census-based summary z-score (238). Covariates were included in the models as potentially influencing estimate of both I and S. All analyses were conducted using the full maximum likelihood method in order to appropriately handle missing data (245) and reported as standardized (STDXY) effects for continuous variables.

Effect Measure Modification

I evaluated possible effect measure modification of the association between long-term exposure to air pollution and trajectories of cognitive decline by age, smoking status, and APOE-ε4 status. Cross-product terms of potential effect modifiers and continuous exposure measures were each included independently in a series of fully adjusted models for each of the four outcomes of interest. Cross-product terms with a p-value <0.15 for either the I or S effect estimates were considered potentially statistically significant and models were then stratified to look at differences between groups.

All data cleaning and descriptive analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC) Latent growth curve analyses were performed using Mplus Version 8 (Muthen & Muthen, Los Angeles, California) (246,247).

RESULTS

Table 3.2 summarizes the baseline characteristics of the cohort. Median age (standard deviation; SD) at time of baseline NP examination was 74.8 ($\pm$9.67) years. The cohort was predominately women (66%). Approximately half of the cohort identified as Hispanic (47%), 28% as non-Hispanic Black, and 23% as non-Hispanic White. On average, participants had 9.5 years of education (SD $\pm$ 4.9). Mean [range] annual exposure estimates to ambient air pollution were 13.2 $\mu g/m^3$ [8.4-16.2] for $PM_{2.5}$, 20.2 $\mu g/m^3$ [3.5-33.7] PM_{10}, and 31.7 ppb [14.0-45.4] NO_2; participants lived an average 303 [7.9-1156.5] meters from a major roadway. Over half of the cohort (56.5%) reported never smoking. In the sub-population of individuals with genetic testing, 1,218 (26.5%) had at least one copy of the APOE-ε4 allele and were considered to be positive for the genetic trait.

Overall, exposure to higher levels of ambient air pollution was highly predictive of cognitive domain scores at baseline but only one pollutant, NO_2, was associated with trajectories of cognitive scores over time. Table 3.3 presents parameter estimates for the intercepts (I) and slopes (S) for global cognition and each of the three functional domains. Adjustment for individual and community level sociodemographic variables attenuated the estimates only slightly. Residential distance to roadway was not strongly associated with either baseline cognitive scores or change in cognition over time.

The relationship between ambient air pollution was significantly modified by an individual's smoking status (Tables 3.3, Appendix Table A.24). The associations between measures of air pollution and global cognitive score were stronger both at baseline (I) and over time (S) among participants who were never smokers versus former or current smokers. Among never smokers, a one IQR increase in $PM_{2.5}$ was predictive of a 0.18 unit lower global cognitive score at baseline (I_{global} = -0.18 $p<0.01$) as compared to a 0.12 unit lower global cognitive score in former/current smokers (I_{global} = -0.12 $p<0.01$). Similarly, a one IQR increase in PM_{10} and NO_2 was predictive of a 0.17 and 0.20-unit lower baseline global cognitive score among never smokers, respectively (PM_{10} I_{global} = -0.17 $p<0.01$; NO_2 I_{global} = -0.120 $p<0.01$). These patterns persisted in changes in global cognitive scores over time. A one IQR increase in PM_{10} was predictive of statistically significantly steeper rates of global cognitive decline score in never smokers (PM_{10} S_{global} = -0.09 $p=0.05$), but not in former/current smokers (PM_{10} S_{global} = -0.02 $p=0.72$). $PM_{2.5}$ and PM_{10} were not statistically significantly associated with global cognitive scores over time, though effect estimates were stronger among never-smokers.

Results from the three individual cognitive domains were similar. Overall, a one IQR increase in $PM_{2.5}$, PM_{10}, and NO_2 was more strongly associated in individuals who had never smoked with lower baseline cognitive scores in each of the three domains. The strongest magnitudes of effect were seen in the executive functioning domain, followed by the language domain. Magnitudes of effect were similar across pollutants. There were minimal associations between pollutant measures and changes in global cognitive score over time (S_{global}) (Table 3.3).

The impact of effect modification by age category was most prominent in the memory and language cognitive domains (Table 3.4, Appendix Table A.24). Among individuals less than 75 years old at baseline, there was a stronger association between a one IQR increase in $PM_{2.5}$,

PM_{10}, and NO_2 and memory domain score at baseline ($PM_{2.5}$ S_{global} = -0.16 ; PM_{10} S_{global} = -0.83 ; NO_2 S_{global} = -0.14, all p <0.01) as compared to individuals 75 years and older ($PM_{2.5}$ S_{global} = -0.05, p<0.01 ; PM_{10} S_{global} = -0.01, p=0.52; NO_2 S_{global} = -0.03, p=0.16). There were minimal associations between measures of air pollution and trajectories of memory scores over time. The pattern of pollutant measures across age categories was similar when assessing language domain scores, with the strongest associations in individuals younger than 75 years old at baseline, with minimal significant associations with language scores over time.

In the sub-population of individuals with genetic testing, being APOE-ε4 positive was independently associated with cognitive trajectories over time (S), but either the presence or absence of the APOE-ε4 allele had no significant influence on cognition at baseline (I) (data not shown). Cross-product terms between measures of pollution and APOE-ε4 status were significant, but when analyses were stratified the effect of air pollution on both baseline and trajectories of decline was significantly only in APOE-ε4 negative individuals. There was no clear pattern of association between APOE-ε4 positive individuals (Table 3.5, Appendix Table A.24).

DISCUSSION

In this urban, population based cohort in Northern Manhattan, I found evidence of an adverse effect of ambient air pollution on the cognitive functioning of older adults consistent with previous research linking air pollution to cognition (114,144,148,150,151,154,155,160,164–181).

In addition, I found strong evidence of effect modification by smoking status and age, but evidence of the presence of the APOE-ε4 allele as an effect modifier between the association of air pollution and cognitive function was inconclusive. In addition to the strengths and limitations specific to the overall analysis and study design, as highlighted in Chapter 2, this investigation of effect modification had several important considerations.

I identified that overall, the effects of ambient air pollution on cognition and cognitive decline were stronger among individuals who never smoked. These results are in contrast to what was found in the Health and Retirement study, where current smokers were found to have worse cognitive function than non-smokers in specific quartiles of exposure (174). There are several substantial differences between the two studies, however, including definition and categorization of exposure and type of neuropsychological testing used. In contrast, an earlier study found that smoking acted as an effect modifier between residential distance to roadway and incident ischemic stroke in the NOMAS population, where the association between proximity to roadways and ischemic stroke was significantly stronger among non-smokers (248). Air pollution has been shown to be associated with many known shared risk factors for both stroke and cognitive decline such as cardiovascular diseases (63,95,96,105,106,228), greater carotid atherosclerotic burden (267,268), and vascular risk factors (123,269). It may also be possible that the association of air pollution and cognition are mediated through these cardiovascular mechanisms and future studies should begin to examine whether these risk factors are mediating both diseases through a similar pathway.

While the search for novel modifiable risk factors is still ongoing, non-modifiable risk factors for cognitive decline have been consistently identified in the literature, with age being the strongest known risk factor (2–4). In this study, age also acted as an effect modifier with the association between air pollution and cognition remaining only in those individuals less than 75 years old at baseline. These results are similar those from a previous study by Ranft et al., which found that living 5-m from a high traffic road was associated with lower CERAD-plus scores only in women <74 years old, with no association in those older than 74 years old (179). It is likely that because age is such a strong predictor of cognitive decline, the relatively small influence of exposure to air pollutants is overshadowed as individuals' age.

Research has suggested there may be a genetic component to cognitive decline, as a family history of dementia as well as the presence of the APOE-ε4 allele are the strongest known predictors of Alzheimer Disease (AD), the most prevalent cause of dementia (2,4,270). An earlier study of autopsied brains by Calderon-Garciduenas suggested that APOE-ε4 carriers could be at higher risk for developing AD if they are exposed to higher levels of air pollutants by showing that APOE-ε4 carriers living in highly polluted areas of Mexico City had accelerated amyloid plaque accumulation as compared to non-carriers (203). Contrary to my hypothesis and the results of the earlier study, I did not observe evidence of a consistent association between air pollution and cognition in models stratified by APOE-ε4 status, despite significant cross-product terms in fully adjusted models. In this combined cohort, the percentage of individuals with homozygous ε4 alleles was very low and therefore individuals heterozygous and homozygous for the ε4 allele were combined into a single group for the purpose of analysis, as done in prior studies (264,265). The odds of developing AD among heterozygous and homozygous carriers is substantially different; individuals heterozygous for the ε4 allele have between 2-4 fold increased odds of developing AD, while homozygous individuals have been shown to have a 5-34 fold increased odds of developing the disease (271,272). These differences in odds of developing Alzheimer Disease and cognitive decline may be causing inconsistent measures of association in stratified models. These null results, however, were consistent with previous population-based epidemiological studies (174). Earlier work done in the WHICAP cohort indicated that the effect of the APOE-ε4allele on cognition varied by racial-ethnic groups (273), however due to power constraints in the LGCM, I could not stratify by racial-ethnic groups in these analyses and this may have also have limited the strength of these findings.

To my knowledge, this is the largest study to analyze effect modification of air pollution cognition and cognitive decline over time in a racially and ethnically diverse sample of over 6,000 older individuals living in an urban area. I found that individuals exposed to higher levels of ambient air pollutants have lower cognition scores at baseline. These associations are stronger among never smokers and the 'younger old'. I didn't find conclusive evidence, however, that APOE-ε4 moderated this relationship. These results further support the current evidence on the role of air pollution on accelerated cognitive aging and brain health; however, the evidence behind effect modification of the relationship between air pollution and cognition is still very limited. Future studies should pay special attention to potential effect modifiers largely to identify potentially vulnerable populations that may be at highest risk for harmful health effects due to air pollution.

TABLES AND FIGURES

Table 3.1 Neuropsychological Test Batteries in the Northern Manhattan Study (NOMAS) and the Washington Heights Inwood Community Aging Project (WHICAP)

Cognitive Function Domain		**NOMAS**	**WHICAP**
Global Cognition Score	**Memory**	Modified California Verbal Learning Test (CVLT) (253)	Selective Reminding Test
	Executive Function	(Color Trails 2 (254,255) - Color Trails 1 (256)), COWAT	
		Odd Man Out, Digit Reordering (257)	Identities and Oddities; Similarities subtest from the Wechsler Adult Intelligence Scale (WAIS)
	Language	Boston Naming (15-item) (258), Animal Naming (259)	
			Comprehension subtest from the Boston Diagnostic Aphasia Exam (BDAE)
	Processing Speed	Color Trails 2 (254,255); Color Trails 1 (256)	
		Grooved Pegboard (260,261), Letter Number Sequencing (262), Symbol Digit Modalities (263)	

Table 3.2 Characteristics of the Combined Northern Manhattan Cohort (n=6,206)	
Sociodemographic Characteristics	**Mean [SD] or n (%)**
Age at baseline, y	74.8 [9.67]
Men	2097 (33.8)
Race-ethnicity	
White non-Hispanic	1426 (23.0)
Black non-Hispanic	1749 (28.2)
Hispanic	2936 (47.3)
Other	95 (1.50)
Years of Education	9.49 [4.90]
Census Z-Score	-2.92 [3.58]
Cardiovascular Risk Factors	
Smoking Status	
Current or Former	2,690 (46.5)
Never	3,495 (56.5)
Hypertension[1]	4761 (76.7)
Diabetes[2]	1,696 (27.2)
Any Cardiac Disease	2,144 (34.6)
APOE-ε4 positive[3] (n=4,594)	1,218 (26.5)
Pollutant Exposures	**Mean [IQR] or n (%)**
$PM_{2.5}$ (μg/m^3)	13.2 [4.46]
PM_{10} (μg/m^3)	20.2 [9.63]
NO_2 (ppb)	31.7 [10.7]
Continuous Residential Distance to Roadway (m)	303.1 [276.7]

IQR indicates interquartile range.
[1]Hypertension = systolic blood pressure > 140 mm/Hg, diastolic blood pressure recording >90 mm/Hg (based on the average of two measurements), physician diagnosis, or self-report, [2]Diabetes=fasting blood glucose ≥ 126 mg/dL, self-report, insulin, or hypoglycemic use [3] Individuals with at least one copy of the APOE-ε4 allele considered positive

Table 3.3 Parameter Estimates of Conditioned Latent Growth Curve Models for the Association between Ambient Air Pollution and Cognition						
	Model 1		**Model 2**		**Model 3**	
	Estimate (SE)	p-value	Estimate (SE)	p-value	Estimate (SE)	p-value
Global Cognitive Score						
PM2.5						
→ I_{global}	-0.18 (0.01)	<0.01	-0.17 (0.01)	<0.01	-0.16 (0.01)	<0.01
→ S_{global}	-0.07 (0.04)	0.08	-0.05 (0.04)	0.25	-0.05 (0.04)	0.22
PM_{10}						
→ I_{global}	-0.16 (0.02)	<0.01	-0.14 (0.01)	<0.01	-0.13 (0.014)	<0.01
→ S_{global}	-0.12 (0.04)	<0.01	-0.06 (0.04)	0.11	-0.06 (0.035)	0.09
NO_2						
→ I_{global}	-0.23 (0.01)	<0.01	-0.18 (0.01)	<0.01	-0.16 (0.01)	<0.01
→ S_{global}	-0.13 (0.04)	0.01	-0.07 (0.04)	0.06	-0.08 (0.04)	0.04
Residential Distance to Roadway						
→ I_{global}	0.06 (0.01)	<0.01	-0.01 (0.01)	0.35	-0.01 (0.01)	0.44
→ S_{global}	0.001 (0.03)	0.98	-0.001 (0.03)	0.98	-0.002 (0.03)	0.94
Memory Domain						
$PM_{2.5}$						
→ I_{mem}	-0.15 (0.01)	<0.01	-0.13 (0.01)	<0.01	-0.11 (0.01)	<0.01
→ S_{mem}	-0.08 (0.04)	0.06	-0.06 (0.04)	0.17	-0.05 (0.04)	0.19
PM_{10}						
→ I_{mem}	-0.11 (0.01)	<0.01	-0.06 (0.01)	<0.01	-0.05 (0.01)	<0.01
→ S_{mem}	0.02 (0.03)	0.56	0.08 (0.03)	0.02	0.08 (0.03)	0.02
NO_2						
→ I_{mem}	-0.17 (0.01)	<0.01	-0.11 (0.01)	<0.01	-0.88 (0.01)	<0.01
→ S_{mem}	-0.03 (0.04)	0.42	0.02 (0.04)	<0.01	0.03 (0.04)	0.47
Residential Distance to Roadway						
→ I_{mem}	0.05 (0.01)	<0.01	0.002 (0.01)	0.85	0.004 (0.01)	0.74
→ S_{mem}	-0.02 (0.03)	0.53	-0.02 (0.03)	0.45	-0.02 (0.03)	0.40
Executive Function Domain						
$PM_{2.5}$						
→ I_{exec}	-0.24 (0.01)	<0.01	-0.25 (0.01)	<0.01	-0.23 (0.01)	<0.01
→ S_{exec}	0.27 (0.13)	0.04	0.38 (0.16)	0.02	0.34 (0.14)	0.02
PM_{10}						

→ I_{exec}	-0.18 (0.02)	<0.01	-0.19 (0.01)	<0.01	-0.17 (0.01)	<0.01
→ S_{exec}	-0.05 (0.07)	0.49	0.09 (0.07)	0.24	0.07 (0.07)	0.32
NO_2						
→ I_{exec}	-0.29 (0.02)	<0.01	-0.25 (0.01)	<0.01	-0.23 (0.01)	<0.01
→ S_{exec}	0.05 (0.08)	0.74	0.19 (0.10)	0.05	0.13 (0.09)	0.14
Residential Distance to Roadway						
→ I_{exec}	0.07 (0.02)	<0.01	-0.01 (0.01)	0.57	-0.01 (0.01)	0.68
→ S_{exec}	0.09 (0.06)	<0.01	0.07 (0.06)	0.27	0.07 (0.06)	0.26
Language Domain						
$PM_{2.5}$						
→ I_{lang}	-0.17 (0.01)	<0.01	-0.17 (0.01)	<0.01	-0.14 (0.01)	<0.01
→ S_{lang}	-0.08 (0.05)	0.10	-0.05 (0.05)	0.28	-0.07 (0.05)	0.18
PM_{10}						
→ I_{lang}	-0.19 (0.01)	<0.01	-0.18 (0.012)	<0.001	-0.16 (0.01)	<0.01
→ S_{lang}	0.14 (0.04)	<0.01	0.19 (0.041)	<0.001	0.18 (0.04)	<0.01
NO_2						
→ I_{lang}	-0.25 (0.02)	<0.01	-0.20 (0.01)	<0.01	-0.16 (0.01)	<0.01
→ S_{lang}	0.14 (0.04)	0.76	0.06 (0.04)	0.19	0.04 (0.05)	0.32
Residential Distance to Roadway						
→ I_{lang}	0.03 (0.01)	0.03	-0.28 (0.01)	0.02	-0.03 (0.01)	<0.01
→ S_{lang}	0.03 (0.03)	0.38	0.03 (0.03)	0.34	0.03 (0.03)	0.37
Model 1: crude model Model 2: Adjusted for individual sociodemographic variables (age, education, sex, race/ethnicity) Model 3: Adjusted for individual and neighborhood sociodemographic variables (Model 2 + Census based SES z-score)						

Table 3.4 Parameter Estimates of Conditioned Latent Growth Curve Models for the Association between Ambient Air Pollution and Cognition, Stratified by Smoking Status				
	Never Smokers		**Former/Current Smokers**	
	Estimate (SE)	p-value	Estimate (SE)	p-value
Global Cognitive Score				
*PM2.5**				
→ I_{global}	-0.18 (0.02)	<0.01	-0.12 (0.02)	<0.01
→ S_{global}	-0.06 (0.06)	0.27	-0.04 (0.06)	0.52
*PM_{10}**				
→ I_{global}	-0.17 (0.02)	<0.01	-0.07 (0.02)	<0.01
→ S_{global}	-0.09 (0.05)	0.05	-0.02 (0.05)	0.72
*NO_2**				
→ I_{global}	-0.20 (0.02)	<0.01	-0.10 (0.02)	<0.01
→ S_{global}	-0.09 (0.05)	0.07	-0.07 (0.06)	0.27
Memory Domain				
*$PM_{2.5}$ **				
→ I_{mem}	-0.13 (0.02)	<0.01	-0.08 (0.02)	<0.01
→ S_{mem}	-0.4 (0.05)	0.49	-0.09 (0.07)	0.20
*PM_{10}**				
→ I_{mem}	-0.09 (0.02)	<0.01	0.01 (0.02)	0.61
→ S_{mem}	0.05 (0.04)	0.19	0.12 (0.06)	0.03
*NO_2**				
→ I_{mem}	-0.12 (0.02)	<0.01	-0.04 (0.02)	0.04
→ S_{mem}	0.03 (0.05)	0.46	0.01 (0.06)	0.86
Executive Function Domain				
*$PM_{2.5}$ **				
→ I_{exec}	-0.26 (0.02)	<0.01	-0.19 (0.02)	<0.01
→ S_{exec}	-0.32 (0.14)	0.03	-0.37 (0.35)	0.29
*PM_{10}**				
→ I_{exec}	-0.20 (0.02)	<0.01	-0.14 (0.02)	<0.01
→ S_{exec}	-0.12 (0.08)	0.81	-0.16 (0.15)	0.28
*NO_2**				
→ I_{exec}	-0.26 (0.02)	<0.01	-0.18 (0.02)	<0.01

→ S_{exec}	0.111 (0.20)	0.26	0.18 (0.19)	0.35
Language Domain				
*$PM_{2.5}$ **				
→ I_{lang}	-0.17 (0.02)	<0.01	-0.10 (0.02)	<0.01
→ S_{lang}	-0.11 (0.06)	0.09	-0.01 (0.08)	0.86
*PM_{10}**				
→ I_{lang}	-0.18 (0.02)	<0.01	-0.12 (0.02)	<0.01
→ S_{lang}	0.12 (0.05)	0.01	-0.26 (0.07)	<0.01
*NO_2**				
→ I_{lang}	-0.20 (0.02)	<0.01	-0.12 (0.02)	<0.01
→ S_{lang}	-0.004 (0.06)	0.95	-0.09 (0.07)	0.23
Model 3: Adjusted for individual and neighborhood sociodemographic variables (age, education, sex, race/ethnicity, Census based SES z-score) *Indicates cross-product term between pollutant and smoking status was significant at p<0.15 level				

Table 3.5 Parameter Estimates of Conditioned Latent Growth Curve Models for the Association between Ambient Air Pollution and Cognition, Stratified by Age Group

	<75 years old		**≥75 years old**	
	Estimate (SE)	p-value	Estimate (SE)	p-value
Global Cognitive Score				
PM2.5				
→ I_{global}	-0.17 (0.02)	<0.01	-0.13 (0.01)	<0.01
→ S_{global}	-0.01 (0.06)	0.89	-0.08 (0.06)	0.18
*PM_{10}**				
→ I_{global}	-0.11 (0.02)	<0.01	-0.15 (0.02)	<0.01
→ S_{global}	0.01 (0.05)	0.84	-0.14 (0.06)	0.01
NO_2				
→ I_{global}	-0.17 (0.02)	<0.01	-0.16 (0.02)	<0.01
→ S_{global}	-0.04 (0.06)	0.49	-0.13 (0.06)	0.04
Memory Domain				
*$PM_{2.5}$ **				
→ I_{mem}	-0.16 (0.02)	<0.01	-0.05 (0.02)	<0.01
→ S_{mem}	0.03 (0.07)	0.71	-0.10 (0.06)	0.09
*PM_{10}**				
→ I_{mem}	-0.83 (0.02)	<0.01	-0.01 (0.02)	0.52
→ S_{mem}	0.15 (0.06)	0.01	0.03 (0.05)	0.52
*NO_2**				
→ I_{mem}	-0.14 (0.02)	<0.01	-0.03 (0.02)	0.16
→ S_{mem}	0.10 (0.06)	0.12	-0.01 (0.05)	0.88
Executive Function Domain				
$PM_{2.5}$				
→ I_{exec}	-0.26 (0.02)	<0.01	-0.19 (0.02)	<0.01
→ S_{exec}	-0.84 (1.67)	0.62	0.15 (0.09)	0.10
*PM_{10}**				
→ I_{exec}	-0.19 (0.02)	<0.01	-0.151 (0.02)	<0.01
→ S_{exec}	-0.321 (0.42)	0.44	-0.09 (0.07)	0.22
NO_2				
→ I_{exec}	-0.25 (0.02)	<0.01	-0.19 (0.02)	<0.01
→ S_{exec}	0.44 (0.78)	0.57	-0.03 (0.08)	0.72

Language Domain				
$PM_{2.5}$ *				
→ I_{lang}	-0.18 (0.02)	<0.01	-0.07 (0.02)	<0.01
→ S_{lang}	-0.12 (0.07)	0.85	-0.14 (0.08)	0.10
*PM_{10}**				
→ I_{lang}	-0.18 (0.02)	<0.01		
→ S_{lang}	0.21 (0.05)	<0.01		
*NO_2**				
→ I_{lang}	-0.20 (0.02)	<0.01	-0.10 (0.02)	<0.01
→ S_{lang}	-0.06 (0.06)	0.34	-0.02 (0.07)	0.82
Model 3: Adjusted for individual and neighborhood sociodemographic variables (age, education, sex, race/ethnicity, Census based SES z-score) *Indicates cross-product term between pollutant and age was significant at p<0.15 level				

Table 3.6 Parameter Estimates of Conditioned Latent Growth Curve Models for the Association between Ambient Air Pollution and Cognition, Stratified by ApoE-4 Status

	APOE-ε4 -		APOE-ε4 +	
	Estimate (SE)	p-value	Estimate (SE)	p-value
Global Cognitive Score				
*PM2.5**				
→ I_{global}	-0.08 (0.02)	<0.01	-0.11 (0.02)	<0.01
→ S_{global}	-0.10 (0.05)	0.04	0.19 (0.12)	0.11
*PM_{10}**				
→ I_{global}	-0.06 (0.02)	<0.01	-0.05 (0.03)	0.08
→ S_{global}	-0.11 (0.04)	<0.01	0.01 (0.09)	0.90
*NO_2**				
→ I_{global}	-0.08 (0.02)	<0.01	-0.09 (0.03)	<0.01
→ S_{global}	-0.137 (0.05)	<0.01	0.03 (0.10)	0.73
Memory Domain				
*$PM_{2.5}$ **				
→ I_{mem}	-0.03 (0.02)	0.08	-0.05 (0.03)	0.06
→ S_{mem}	-0.11 (0.05)	0.03	0.05 (0.10)	0.58
*PM_{10}**				
→ I_{mem}	-0.003 (0.02)	0.86	0.02 (0.03)	0.54
→ S_{mem}	0.04 (0.04)	0.26	0.14 (0.07)	0.04
*NO_2**				
→ I_{mem}	-0.02 (0.02)	0.25	-0.04 (0.03)	0.173
→ S_{mem}	-0.03 (0.04)	0.51	-0.13 (0.08)	0.13

Model 3: Adjusted for individual and neighborhood sociodemographic variables (age, education, sex, race/ethnicity, Census based SES z-score)
*Indicates cross-product term between pollutant and APOE-ε4 status was significant at p<0.15 level

CONCLUSIONS.

Age-related cognitive decline is a growing public health concern as increases in life expectancy are expected to substantially increase the prevalence of cognitive impairment and dementia (226). An estimated 46.8 million individuals are living with dementia, with the global prevalence expected to double every 20 years (1). Poor cognitive function is a key cause of disability among older adults and can have profound social, economic, and health implications (139,227). Global healthcare expenditures for cognitive impairment reached 818 billion dollars in 2015 and are expected to reach a staggering two trillion dollars by 2030 (1). Risk of accelerated cognitive decline increases with age, cerebrovascular disease, and presence of traditional cardiovascular risk factors, but these factors do not fully account for risk of cognitive decline in the population. Identification of novel risk factors is therefore of great importance. Long-term exposure to ambient air pollution has recently been highlighted as a risk factor for cognitive decline in addition to its association with other cardiovascular and neurological outcomes (166,173,175).

Air pollution, a largely ubiquitous environmental exposure, is rapidly becoming a widespread public health hazard, particularly in urban areas. Despite significant decreases in overall levels of ambient air pollution over the last decade, levels remain high. As of 2011, 124 million United States residents were living in areas that did not meet the US Environmental Protection Agency (EPA) National Ambient Air Quality Standards (49). While only recently implicated as a modifiable risk factor for cognitive decline, the concern over adverse health effects of air pollution is not new.

Studies have suggested older adults are particularly vulnerable to the health effects of adverse environmental exposures, which cause amplified respiratory and cardiovascular symptoms, exacerbations of existing diseases, and increased mortality (55–57). Long-term exposure to pollution has been associated with increased risk of incident cardiovascular disease (CVD) (95,96,105), acute myocardial infarction (MI)(228), heart failure (63,106), and death (97,114–118,120,121), with several large cohort studies highlighting the association between fine particulate matter exposure and overall CVD mortality (67,97–103). The evidence linking air pollution with the cardiovascular and cerebrovascular systems suggest it may also have a damaging impact on the brain and cognitive processes, but research on the effects of pollution on the nervous system, particularly in older adults, is limited (136–138).

The aim of this dissertation was to fill specific knowledge gaps related to environmental exposures, particularly long-term exposure to air pollution, and its influence on cognitive decline in the aging population. As part of this investigation, a comprehensive, structured review of the existing literature on air pollution and cognitive function was conducted. The existing evidence between ambient air pollution and cognition was highly suggestive of an association, with all studies reporting at least one adverse association. It is clear, however, that these studies on cognitive function and decline have not been performed or analyzed in a homogenous way. There were substantial differences in study design, population, methodology, and measurement of both exposure and outcome that make direct comparisons across studies difficult and make it difficult to identify a true association. Identified data inconsistency and knowledge gaps spoke to the need for comprehensive analyses with longitudinal data in order to begin to examine true trajectories of cognitive decline. In addition, many of the current studies were not generalizable to an urban aging population that may be most at risk of the effects of air pollution, speaking to the need for use of a racially and ethnically diverse population-based cohort not limited by sex.

In order to begin to address the limitations of current studies and add to the knowledge base supporting the association between ambient air pollution and cognitive decline, I brought together two prospective, population-based cohorts, the Northern Manhattan Study (NOMAS) and the Washington Heights Inwood Community Aging Project (WHICAP) to study the association between exposure to ambient air pollution and age-related cognitive decline.

The NOMAS and WHICAP cohorts included in this dissertation provided a unique opportunity to evaluate multi-dimensional data in a population of over 6,000 residents of Northern Manhattan. Neuropsychological (NP) batteries used in NOMAS and WHICAP were very similar; both were designed to capture key cognitive domains in both English and Spanish speaking older adults and developed to permit the calculation of z-scores that allow for measure of global cognition as well as cognitive domain-specific analyses. Additionally, serial NP testing allows for the analysis of cognitive decline over time. Several measure of long-term exposure to air pollution was measured using exposure estimates for $PM_{2.5}$, PM_{10}, and NO_2 generated from the Multi-Ethnic Study of Atherosclerosis and Air Pollution Study (MESA-Air). The use of several measures of pollution allowed for comparison across exposures and helped to identify a pattern of effect. Exposure status was assigned to participants based on reconstructed address histories, so as to mitigate potential measurement error, a common issue in current studies. In addition, these cohorts allowed for the assessment of effect measure modification by behavioral and genetic factors, and the identification of high risk groups. Using this uniquely qualified study population, **I first investigated the association between long-term exposure to ambient air pollution and cognitive decline among older adults in an urban population within Northern Manhattan.** I then set out to **assess specific mechanisms involved in the association between long-term exposure to ambient air pollution and cognitive decline, specifically investigating the APOE-ε4 allele, age, and current smoking behavior as effect modifiers of the association between long-term exposure to ambient air pollution and cognitive decline.**

In this urban, population based cohort in Northern Manhattan, I found evidence of an adverse effect of ambient air pollution on the cognitive functioning of older adults. Overall, exposure to higher levels of ambient air pollution was highly predictive of cognitive domain scores, but at baseline only. Estimates of effect of air pollutants on global cognitive scores were similar across all three measures of pollution. A one IQR increase in $PM_{2.5}$ was predictive of a 0.16 unit lower global cognitive score at baseline. Similarly, a one IQR increase in PM_{10} and NO_2 was predictive of a 0.13 and 0.16-unit lower baseline global cognitive score, respectively. Results from three functional cognitive domains (memory, executive function, and language) were similar, with a one IQR increase in $PM_{2.5}$, PM_{10}, and NO_2 significantly associated with lower baseline cognitive scores. The patterns of association were similar across both pollutant types and cognitive domains in this aging, urban population. Contrary to my hypothesis, limited evidence was found between estimates of air pollution and trajectories of cognitive decline.

I then expanded on these findings by testing the hypothesis that both genetic and behavioral risk factors have an association with cognition and are able to modify the air pollution-cognition relationship. I examined two previously tested modifiers, age and smoking status among older adults in an urban population within Northern Manhattan. In a subset of study participants with available genetic data, I also examined whether the presence of heterogeneous APOE-ε4 alleles modified this association.

I found strong evidence of effect modification by smoking status, where contrary to the hypothesis; the overall effects of ambient air pollution on cognition and cognitive decline were stronger among individuals who never smoked. Among never smokers, a one IQR increase in $PM_{2.5}$ was predictive of a 0.18 unit lower global cognitive score at baseline as compared to a 0.12 unit lower global cognitive score in former/current smokers. Similarly, a one IQR increase in PM_{10} and NO_2 was predictive of a 0.17 and 0.20-unit lower baseline global cognitive score among never smokers, respectively. These patterns persisted in changes in global cognitive scores over time. A one IQR increase in PM_{10} was predictive of statistically significantly steeper rates of global cognitive decline score in never, but not in former/current smokers. $PM_{2.5}$ and PM_{10} were not statistically significantly associated with global cognitive scores over time; however effect estimates were stronger among never-smokers. Results from the three individual functional cognitive domains were similar. Overall, a one IQR increase in $PM_{2.5}$, PM_{10}, and NO_2 was more strongly associated in individuals who had never smoked with lower baseline cognitive scores in each of the three domains.

The impact of effect modification by age category was most prominent in the memory and language cognitive domains. Among individuals less than 75 years old at baseline, there was a stronger association between a one IQR increase in $PM_{2.5}$, PM_{10}, and NO_2 and memory domain score at baseline as compared to individuals 75 years and older. There were minimal associations between measures of air pollution and trajectories of memory scores over time. The pattern of pollutant measures across age categories was similar when assessing language domain scores, with the strongest associations in individuals younger than 75 years old at baseline, with minimal significant associations with language scores over time.

Contrary to my hypothesis, I did not observe evidence of a clear association between air pollution and cognition in models stratified by APOE-ε4 status. While these results contrasted with earlier autopsy-based studies (203), the null results were consistent with previous population-based epidemiological studies (174).

The current study adds to the growing scientific evidence supporting the importance of exposure to air pollution in aging brain health, however, this analysis had several important limitations that have been described in detail in earlier chapters. A key limitation is the limited geographical extent of the Northern Manhattan study area which may have led to limited variability in exposure levels. I attempted to attenuate this issue by combining the two cohorts, which led to wider ranges in exposure estimates as compared to earlier studies (135,248). Another limitation is that the estimates of air pollution used in the current study are indirect and based on spatiotemporal modeling from monitors located throughout the study area. In addition, because the estimates are based on residential geocoded locations, they don't account for any time spent outside of the home. Lastly, there may have been further misclassification of exposure due to individuals moving throughout the study period. In this dissertation analysis, I have attempted to mitigate any bias due to methodological difficulties in defining and estimating long-term measures of exposure to air pollution by categorizing pollution in multiple ways, and measuring several different components of air pollution. I also performed sensitivity analyses to attempt to quantify any bias brought on by limiting the analytical sample to those individuals who had not moved over the study period. Measurement error due to these biases would likely be non-differential, attenuating our estimates, and therefore the effects of air pollution found here would likely be true.

The lack of effect of ambient air pollution on trajectories of cognitive decline may have been due to several methodological limitations specifically impacting the analysis of cognition over time. This study analyzed the effect of air pollution on trajectories of change using only baseline measures of exposure, and not exposure over time. The use of pollutant estimates at one year prior to baseline NP Examination may have been a better estimate of exposure in the years prior to the study, and the estimates of association may actually be measuring the effect of pollution on cognition much earlier in life. Future studies should examine this further using longitudinally measured pollutants to see if that better explains the cognitive changes over time in aging populations. In addition, a second limitation is the fact that many of the physiological processes preceding cognitive decline have been found to begin much earlier in life, and risk factors at midlife have been shown to be more important for process of accelerated cognitive decline (1,26,27,31,33). Exposure to pollutants earlier in life may be more important than that in an individual's older years, therefore the measures that are being used in this study may not be accurately measuring relevant exposure times. Assessing midlife environmental risk factors is not possible in these two cohorts, but the results from the proposed study can be used to inform future studies which better look at a life course approach of environmental effects on cognitive aging. A final limitation that may be causing these null associations over time is an ascertainment bias inherent in these two longitudinal cohorts. The use of the LGCM models in this analysis allowed me to keep in all individuals, regardless of number of NP examinations they completed. It is likely, however, that the individuals that both survived and continued to return for up to 6 rounds of cognitive testing were more healthy and cognitively intact than individuals with less than 6 exams. This bias would likely move the effects of air pollution over time towards the null, making it difficult to see any influence of exposure on trajectories of decline.

I was unable to adjust for individual SES or income in this study due to limitations in the available data, however this is likely to also have played a role in the differences in association with air pollution and baseline cognition versus cognitive decline. It is well established that individuals with lower education and SES have lower cognition over the life course and subsequently have attenuated trajectories of decline. Individuals in this population had on average only 9 years of education, and many received that education outside of the United States. It's possible that in this study, the effects of air pollution on trajectories of decline were tempered due to the fact that these individuals were beginning at a lower level of cognition and therefore did not have significant decline in trajectories of cognition over time.

These studies observed consistent associations with a series of measures of ambient air pollutants. A key issue in studies measuring the health effects of air pollution, however, is that individual pollutants don't exist in isolation and it is difficult, if not impossible, to truly differentiate individual pollutant effects in large epidemiologic studies due to constant chemical reactions that occur between pollutants (58). The major pollutants examined in this study are present together but distributions in the pollutant mixture may vary by location, source of toxin, weather patterns, or season of the year. To date, there are no studies which examine the effect of the complete mixture on cognitive health. Future studies analyzing pollutant measures as a mixture would not only allow for analysis of real life exposure experience, but will also identify key components of urban air pollution that have the strongest effects on health to be validated in future studies. Analysis of air pollution as a mixture instead of individual pollutants may also begin to explain variability of findings across studies.

A final important limitation of this study overall is the potential for measurement error of the outcome, which may be further compounded by the combination of two individual cohorts. All cognitive testing was performed by trained research assistants in the two studies, introducing the potential for variability across individual interviewers in the way that the cognitive testing was implemented and scored. While research assistants in both studies underwent similar training, there is also likely some variation in interviewing process that varies between cohorts. In addition, most of the WHICAP NP examinations were performed in participant's homes, while the NOMAS testing was performed in a clinic setting, also adding to potential cohort effects in measurement of cognition. Lastly, the results of cognitive tests may vary significantly from one examination to the other due to the participant's mood, energy level, health status, location of interview, or relationship with the interviewer.

Regardless, the study population used in this study provided a unique opportunity to evaluate multi-dimensional data in a population of over 6,000 residents of Northern Manhattan and there are several key strengths to this dissertation. Combining two large, prospective cohorts, NOMAS and WHICAP, has led to the largest longitudinal analyses of ambient air pollution and cognitive decline to date. In addition, the use of these two cohorts has several benefits over many of the current studies.

Earlier studies have shown that the prevalence of cognitive decline and dementia is higher in women (185,186) and non-Hispanic whites (187–193), while older African Americans are twice as likely and Hispanics are 1.5 times as likely as older non-Hispanic whites to develop incident dementia (187–193). The use of a racially and ethnically diverse population of older adults, not limited by sex, allows the results of this dissertation to be generalizable to an aging urban population at highest risk for the health effects of air pollution.

The evidence behind the mechanisms through which air pollution impacts cognitive function is limited. This study is one of the first to begin to examine potential effect modification of the association between air pollution and cognition and brain health in an attempt to identify groups at potentially higher risk for the adverse health effects of this exposure, with mixed results. It is feasible, however, that many of the cardiovascular risk factors often analyzed as moderators or confounders, may actually mediate the relationship between air pollution and cognitive decline.

As previously discussed, evidence suggests that brain health is very closely linked to the health of the cardiovascular system, thus sharing many of the same lifestyle and psychosocial risk factors (3,15–29). In addition, exposure to air pollution has been linked to an increased risk of many of these factors (123–130). Future studies should begin to examine these factors as potential mediators along the pathway between ambient air pollution and cognitive function.

In conclusion, as global life expectancy continues to increase, the rates of age-related cognitive decline and dementia are expected to skyrocket. To date, there is no current consensus on key modifiable risk factors are for cognitive decline; therefore, the identification of novel risk factors is of great importance. This dissertation will help to fill knowledge gaps related to environmental exposures, particularly long-term exposure to air pollution, and its influence on cognitive decline. This study found that individuals exposed to higher levels of ambient air pollutants have lower cognition scores at baseline, however there is no evidence that presence of these pollutants cause individuals to decline more rapidly over time. These associations are stronger among never smokers and the 'younger old'. These results further support the current evidence on the role of air pollution on accelerated cognitive aging and brain health.

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APPENDIX.

Chapter 3. Supplementary Methods

Harmonization of Neuropsychological Batteries across Cohorts

NP batteries used in NOMAS and WHICAP were very similar; both were designed to capture key cognitive domains in both English and Spanish speaking older adults and developed to permit the calculation of domain-specific Z-scores that allow for efficient cross-cohort harmonization for combined analysis due to a large number of overlapping tests. Cognitive decline was measured in two ways: (1) trajectories of change in global cognition scores and (2) trajectories of performance in individual cognitive domains.

In order to utilize all available NP data for each cohort, I harmonized available tests across the two studies. All NP tests were first standardized into z-scores using combined cohort-specific means and standard deviations at baseline. I chose not to adjust for age, education, or race/ethnicity as done in prior studies so that these variables can be analyzed as confounders in order to be able to ascertain the independent effects of these covariates on cognition. Exploratory factor analyses had been performed previously in each of the individual cohorts to identify cognitive functional domains (14,231,237). To confirm that the NP data from this combined cohort still fit into the previously identified factor structure, I performed a confirmatory factor analysis identifying four key functional domains (Table A.1). Performance in each of these four identified domains was expressed as the weighted mean of the individual test z-scores loading into that domain. Weights were calculated using the factor scores of the confirmatory factor analysis. A global cognition score was constructed using the weighted mean of the z-scores of all NP Tests used to calculate the functional domains and was used as the primary outcome to summarize the overall association of air pollution exposure on cognitive performance. When analyzing the processing speed domain, I found that the adjusted models did not converge, due to a large amount of missing data in the NP tests used to calculate that domain. Therefore, I chose to include those tests, where available, in the global measure of cognition but did not analyze processing speed as an independent cognitive domain.

Latent Growth Curve Model Fit

I first ran a series of unconditional LGCM models (Model 0) for each of the four outcomes of interest (global cognition, executive function, memory, and language) in which I assessed the influence of varying fixed and random effects, and linear and quadratic trends over time. The selection of the best model was based on the Schwartz Bayesian information criterion (BIC), with lower values indicating better fit. Upon identifying the best base model fit, I then allowed for up to three latent trajectory classes. Accuracy of classification into distinct trajectory classes was assessed using entropy values ranging from 0 to 1, with values closer to 1 corresponding to better classification accuracy. I assessed individual model fit using the following indices: Chi-square (x^2); comparative fit index (CFI), Tucker Lewis Index (TLI); Root Mean Square Error of Approximation (RMSEA) with 90% confidence intervals; and the Standardized Root Mean Residual (SRMR). Based on prior studies, I will use CFI and TLI values greater than 0.90 and RMSEA values less than 0.08, and an non-significant Chi-square value to identify an appropriately fit model (241).

After comparing models I identified the best fit model to be one that allowed for random effects of both the intercept and slope, and included a quadratic term for time (Table A.3). Increasing the number of trajectory classes decreased the BIC, however upon applying a restriction that there must be at least 5% of participants in a class to be meaningful clinically and numerically stable (242), I chose a one-class model as the best fit. Overall, model fit statistics of the unconditional LGCM for each outcome were acceptable. The Chi-square value was significant for each, indicating an inappropriate model fit, however, the significance of the Chi-square test is very sensitive to sample size with small differences found to be significant in large samples (243). In contrast, other fit indices suggested a well fit model (Table A.4).

Sensitivity Analyses. I ran a series of sensitivity analyses in an attempt to ascertain and quantify bias at several points throughout the study. A key limitation in the analysis of longitudinal cohort studies is subject ascertainment and the impact of subject dropout and death. I have attempted to address this in several ways. A benefit of using LGCM models to assess trajectories of decline is that there is no need to remove individuals with only one NP Examination as they will still contribute to the calculation of the latent intercept. However, there are likely reasons that individuals drop out of a study early that are related to the outcome, particularly for cognitive dysfunction and dementia. If these individuals are only contributing to the intercept, they may bias the analyses. I addressed this by doing a sensitivity analysis including only those with 2 or more NP examinations. Results of these models were not substantially different from those in the full cohort (Appendix Table A.22). I next re-ran all models excluding all participants who had died prior to undergoing 6 NP examinations in an attempt to mitigate death as a competing risk. Air pollution is a known cause of death and therefore could be increasing the risk of death in this population before any cognitive symptoms begin to manifest. Despite 38% of participants dying before completion of the study, limitation of the population did not change the overall results of the analyses (Appendix Table A.23). Another area for potential bias in this analysis was misclassification of exposure due to individuals moving throughout the study period. Some studies have tried to mitigate this bias by including only those participants identified as either movers or non-movers. In this study, I found that a substantial percentage of the combined cohort (58%) did not have available baseline residential data (Waves II and III of the WHICAP Study), therefore could not be identified as 'non-movers'. In individuals with complete baseline data, I found that 91% of them did not move throughout the study period. The LGCMs on the sample of non-movers with available data did not converge and therefore could not be compared to the results of the full cohort. Given that the sampling of the cohort did not change over time, there is no reason to believe that individuals with complete residential data are substantially different than those without and so it can be expected that there is limited residential mobility in those individuals as well. In addition, any measurement error arising from those individuals moving throughout the study period is expected to be non-differential and therefore bias the effects of the analysis towards the null.

TABLES AND FIGURES

Table A.1 Standardized Factor Loading Scores for Confirmatory Factor Analysis of Neuropsychological Tests across NOMAS and WHICAP Cohorts.				
	Executive Function	**Memory**	**Processing Speed**	**Language**
	Factor Loading (SE)			
Color Trails: Trails 2 - Trails 1	0.463 (0.022)			
Digit Ordering Test: Total Correct	0.676 (0.053)			
Odd Man Out: Trial 2 + Trial 4	0.685 (0.050)			
WAIS-R: Similarities Raw	0.769 (0.029)			
Mattis Dementia Rating Scale: Identities/Similarities Total	0.519 (0.022)			
Verbal Learning Test: Trial 1-5 Recall		0.855 (0.013)		
Verbal Learning Test: Delay Recall		0.890 (0.013)		
Verbal Learning Test: Recog - (RL + UL False Pos)		0.683 (0.020)		
Selective Reminding Test: Total Recall		0.908 (0.005)		
Selective Reminding Test: Delayed Recall		0.832 (0.006)		
Benton Recognition		0.494 (0.012)		
Selective Reminding Test: Delayed Recognition		0.576 (0.010)		
Color Trails: Trails 1			0.837 (0.008)	
Color Trails: Trails 2			0.867 (0.008)	
Grooved Pegboard: Non Dom Time			0.740 (0.020)	
Grooved Pegboard: Dom Time			0.773 (0.019)	
WAIS: Letter Number Sequencing			0.741 (0.039)	
Category Fluency: Animal Naming				0.717 (0.008)
Controlled Oral Word Association: CFL				0.753 (0.008)

Boston Naming: Spontaneous Correct				0.574 (0.010)
Boston Diagnositc Aphasia Exam: Comprehension				0.523 (0.011)
All factor scores significant at a $p<0.05$ level. Bolded tests indicate overlapping tests.				

Table A.2 Participants with NP examination data at each time point		
	N	**%**
Baseline NP	6,206	100
NP Exam 2	4,681	75.43
NP Exam 3	2,659	42.85
NP Exam 4	1,682	27.10
NP Exam 5	1,054	16.98
NP Exam 6	**744**	**11.99**
NP Exam 7	432	6.96
NP Exam 8	224	3.61
NP Exam 9	125	2.01
NP Exam 10	70	1.13
NP Exam 11	43	0.69
NP Exam 12	14	0.23
NP Exam 13	6	0.10

Table A.3 Exploratory Model Fit Results to Identify Best Fit Unconditional Latent Growth Curve Model						
Model	**BIC**	**Classes**	**Entropy**	**Proportion of Individuals in Class**		
				1	**2**	**3**
Global Cognitive Score, Unconditional Model						
Random I and S	9085.42	1		1.00	---	---
Random I, fixed S	9461.43	1		1.00	---	---
Fixed I, fixed S	18965.91	1		1.00	---	---
Random I, S, and Q	9058.79	1		1.00	---	---
	8537.40	2	0.88	0.030	0.97	---
	8289.80	3	0.82	0.025	0.05	0.93
Memory Domain Score, Unconditional Model						
Random I and S	24409.24	1		1.00	---	---
Random I, fixed S	24741.26	1		1.00	---	---
Fixed I, fixed S	33416.06	1		1.00	---	---
Random I, S, and Q	24358.77	1		1.00	---	---
	24083.10	2	0.78	0.96	0.04	---
	23968.99	3	0.83	0.95	0.04	0.01
Executive Domain Score, Unconditional Model						
Random I and S	14770.05	1		1.00	---	---
Random I, fixed S	14804.12	1		1.00	---	---
Fixed I, fixed S	21354.39	1		1.00	---	---
Random I, S, and Q	14791.84	1		1.00	---	---
	14588.88	2	0.55	0.80	0.20	---
	14458.77	3	0.67	0.78	0.21	0.12
Language Domain Score, Unconditional Model						
Random I and S	13164.89	1		1.00	---	---
Random I, fixed S	13336.60	1		1.00	---	---
Fixed I, fixed S	25005.95	1		1.00	---	---
Random I, S, and Q	13127.76	1		1.00	---	---
	12890.06	2	0.90	0.01	0.99	---
	12637.58	3	0.94	0.99	0.01	0.001
BIC: Bayesian Information Criteria; RMESA: Root Mean Square Error of Approximation; SRMR: Standardized Root Mean Residual; CFI: Comparative Fit Index; TLI: Tucker Lewis Index; I:Intercept; S: Slope; Q: Quadratic term for fit						

Table A.4 Final Model Specifications and Fit Indices for Unconditional Latent Growth Curve Models				
	Global Cognition Score	**Executive Function Domain Score**	**Memory Domain Score**	**Language Domain Score**
Final Model Specification	Random intercept (I), random slope (S), with quadratic term (Q)			
Classes	1	1	1	1
BIC	9058.79	14791.84	24358.77	13127.76
Chi-Square				
Value	25.93	32.084	52.081	38.695
p-value	0.01	<0.01	<0.01	<0.01
RMSEA				
Estimate	0.014	0.017	0.023	0.019
90% CI	0.006, 0.021	0.010, 0.024	0.017, 0.030	0.013, 0.026
SRMR	0.02	0.022	0.026	0.018
CFI	0.999	0.995	0.993	0.995
TLI	0.998	0.993	0.991	0.994
BIC: Bayesian Information Criteria; RMESA: Root Mean Square Error of Approximation; SRMR: Standardized Root Mean Residual; CFI: Comparative Fit Index; TLI: Tucker Lewis Index				

Table A.5 Parameter Estimates of Conditioned Latent Growth Curve Models for the Association between $PM_{2.5}$ and Global Cognitive Decline

	Model 1		Model 2		Model 3	
	Estimate (SE)	p-value	Estimate (SE)	p-value	Estimate (SE)	p-value
I_{global} mean	0.99 (0.07)	<0.01	1.20 (0.052)	<0.01	3.39 (0.14)	<0.01
S_{global} mean	-0.16 (0.25)	0.51	0.25 (0.031)	<0.01	3.83 (0.51)	<0.01
I_{global} variance	0.97 (0.01)	<0.01	0.07 (0.003)	<0.01	0.61 (0.01)	<0.01
S_{global} variance	0.99 (0.01)	<0.01	0.003 (0.001)	<0.01	0.80 (0.04)	<0.01
I/S covariance	0.12 (0.05)	0.01	0.001 (0.001)	0.51	0.04 (0.06)	0.72
PM2.5						
→ I_{global}	-0.18 (0.01)	<0.01	-0.17 (0.01)	<0.01	-0.16 (0.01)	<0.01
→ S_{global}	-0.07 (0.04)	0.08	-0.05 (0.04)	0.25	-0.05 (0.04)	0.22
Covariates						
Age → I_{global}			-0.27 (0.01)	<0.01	-0.27 (0.01)	<0.01
Age → S_{global}			-0.42 (0.04)	<0.01	-0.42 (0.04)	<0.01
Education → I_{global}			0.36 (0.01)	<0.01	0.36 (0.01)	<0.01
Education → S_{global}			0.06 (0.04)	0.09	0.06 (0.04)	0.09
Male → I_{global}			-0.05 (0.01)	<0.01	-0.05 (0.01)	<0.01
Male → S_{global}			0.02 (0.03)	0.44	0.02 (0.03)	0.44
Black Non-Hispanic → I_{global}			-0.21 (0.02)	<0.01	-0.16 (0.02)	<0.01
Black Non-Hispanic → S_{global}			0.01 (0.0)	0.88	-0.002 (0.04)	0.95
Hispanic → I_{global}			-0.34 (0.02)	<0.01	-0.28 (0.020)	<0.01
Hispanic → S_{global}			0.04 (0.04)	0.31	0.03 (0.05)	0.47
Other Race → I_{global}			-0.07 (0.01)	<0.01	-0.06 (0.01)	<0.01
Other Race → S_{global}			0.06 (0.02)	<0.01	0.06 (0.02)	<0.01
Z-SES score → I_{global}					0.10 (0.01)	<0.01
Z-SES score → S_{global}					-0.01 (0.04)	0.72
Parameters	15		27		29	
TLI	0.990		0.990		0.990	
CFI	0.988		0.992		0.993	
SRMR	0.042		0.025		0.023	
RMESA (90% CI)	0.026 (0.020-0.031)		0.018 (0.014-0.021)		0.017 (0.013,0.020)	

Model 1: crude model; Model 2: Adjusted for individual sociodemographic variables (age, education, sex, race/ethnicity) Model 3: Adjusted for individual and neighborhood sociodemographic variables (Model 2 + Census based SES z-score)

Table A.6 Parameter Estimates of Conditioned Latent Growth Curve Models for the Association between PM_{10} and Global Cognitive Decline						
	Model 1		**Model 2**		**Model 3**	
	Estimate (SE)	p-value	Estimate (SE)	p-value	Estimate (SE)	p-value
I_{global} mean	0.44 (0.05)	<0.01	2.87 (0.14)	<0.01	2.82 (0.14)	<0.01
S_{global} mean	-0.21 (0.12)	0.07	3.60 (0.45)	<0.01	3.64 (0.46)	<0.01
I_{global} variance	0.98 (0.01)	<0.01	0.63 (0.01)	<0.01	0.62 (0.01)	<0.01
S_{global} variance	0.99 (0.01)	<0.01	0.81 (0.04)	<0.01	0.81 (0.04)	<0.01
I/S covariance	0.11 (0.05)	0.02	0.02 (0.06)	0.67	0.03 (0.06)	0.62
PM_{10}						
→ I_{global}	-0.16 (0.02)	<0.01	-0.14 (0.01)	<0.01	-0.13 (0.014)	<0.01
→ S_{global}	-0.12 (0.04)	<0.01	-0.06 (0.04)	0.11	-0.06 (0.035)	0.09
Covariates						
Age → I_{global}			-0.26 (0.01)	<0.01	-0.26 (0.01)	<0.01
Age → S_{global}			-0.41 (0.04)	<0.01	-0.41 (0.04)	<0.01
Education → I_{global}			0.35 (0.02)	<0.01	0.34 (0.01)	<0.01
Education → S_{global}			0.06 (0.04)	0.11	0.06 (0.04)	0.12
Male → I_{global}			-0.06 (0.01)	<0.01	-0.06 (0.01)	<0.01
Male → S_{global}			0.02 (0.03)	-0.44	0.02 (0.03)	0.43
Black Non-Hispanic → I_{global}			-0.22 (0.02)	<0.01	-0.16 (0.02)	<0.01
Black Non-Hispanic → S_{global}			0.01 (0.03)	0.85	-0.01 (0.04)	0.98
Hispanic → I_{global}			-0.36 (0.02)	<0.01	-0.28 (0.02)	<0.01
Hispanic → S_{global}			0.04 (0.04)	0.32	0.03 (0.05)	0.48
Other Race → I_{global}			-0.07 (0.01)	<0.01	-0.06 (0.01)	<0.01
Other Race → S_{global}			0.06 (0.02)	<0.01	0.06 (0.02)	<0.01
Z-SES score → I_{global}					0.12 (0.01)	<0.01
Z-SES score → S_{global}					-0.01 (0.04)	0.78
Parameters	15		29		29	
TLI	0.99		0.99		0.99	
CFI	0.99		0.99		0. 99	
SRMR	0.04		0.03		0.02	
RMESA (90% CI)	0.023 (0.018, 0.028)		0.016 (0.012, 0.020)		0.015 (0.011, 0.019)	

Model 1: crude model
Model 2: Adjusted for individual sociodemographic variables (age, education, sex, race/ethnicity)
Model 3: Adjusted for individual and neighborhood sociodemographic variables (Model 2 + Census based SES z-score)

Table A.7 Parameter Estimates of Conditioned Latent Growth Curve Models for the Association between NO_2 and Global Cognitive Decline

	Model 1		Model 2		Model 3	
	Estimate (SE)	p-value	Estimate (SE)	p-value	Estimate (SE)	p-value
I_{global} mean	1.09 (0.07)	<0.01	3.29 (0.14)	<0.01	3.19 (0.14)	<0.01
S_{global} mean	0.07 (0.19)	0.71	3.84 (0.48)	<0.01	3.87 (0.49)	<0.01
I_{global} variance	0.95 (0.01)	<0.01	0.62 (0.01)	<0.01	0.61 (0.01)	<0.01
S_{global} variance	0.98 (0.01)	<0.01	0.80 (0.04)	<0.01	0.80 (0.04)	<0.01
I/S covariance	0.11 (0.05)	0.02	0.02 (0.05)	0.66	0.03 (0.05)	0.63
NO_2						
→ I_{global}	-0.23 (0.01)	<0.01	-0.18 (0.01)	<0.01	-0.16 (0.01)	<0.01
→ S_{global}	-0.13 (0.04)	0.01	-0.07 (0.04)	0.06	-0.08 (0.04)	0.04
Covariates						
Age → I_{global}			-0.26 (0.01)	<0.01	-0.26 (0.01)	<0.01
Age → S_{global}			-0.41 (0.04)	<0.01	-0.41 (0.04)	<0.01
Education → I_{global}			0.35 (0.01)	<0.01	0.35 (0.01)	<0.01
Education → S_{global}			0.06 (0.04)	0.13	0.06 (0.04)	0.12
Male → I_{global}			-0.06 (0.01)	<0.01	-0.06 (0.01)	<0.01
Male → S_{global}			0.02 (0.03)	0.45	0.02 (0.03)	0.46
Black Non-Hispanic → I_{global}			-0.21 (0.02)	<0.01	-0.16 (0.02)	<0.01
Black Non-Hispanic → S_{global}			0.01 (0.03)	0.77	-0.003 (0.05)	0.94
Hispanic → I_{global}			-0.33 (0.02)	<0.01	-0.28 (0.01)	<0.01
Hispanic → S_{global}			0.05 (0.04)	0.28	0.03 (0.05)	0.51
Other Race → I_{global}			-0.07 (0.01)	<0.01	-0.06 (0.01)	<0.01
Other Race → S_{global}			0.06 (0.02)	<0.01	0.06 (0.02)	<0.01
Z-SES score → I_{global}					0.09 (0.02)	<0.01
Z-SES score → S_{global}					-0.03 (0.04)	0.47
Parameters	15		27		29	
TLI	0.990		0.992		0.992	
CFI	0.992		0.994		0.994	
SRMR	0.043		0.024		0.023	
RMESA (90% CI)	0.023 (0.017, 0.028)		0.015 (0.012, 0.019)		0.015 (0.011, 0.018)	

Model 1: crude model
Model 2: Adjusted for individual sociodemographic variables (age, education, sex, race/ethnicity)
Model 3: Adjusted for individual and neighborhood sociodemographic variables (Model 2 + Census based SES z-score)

Table A.8 Parameter Estimates of Conditioned Latent Growth Curve Models for the Association between Residential Distance to Roadways and Global Cognitive Decline						
	Model 1		**Model 2**		**Model 3**	
	Estimate (SE)	p-value	Estimate (SE)	p-value	Estimate (SE)	p-value
I_{global} mean	-0.06 (0.01)	<0.01	2.70 (0.139)	<0.01	2.66 (0.14)	<0.01
S_{global} mean	-0.62 (0.07)	<0.01	3.39 (0.445)	<0.01	3.43 (0.45)	<0.01
I_{global} variance	0.99 (0.002)	<0.01	0.65 (0.013)	<0.01	0.63 (0.01)	<0.01
S_{global} variance	1.00 (0.001)	<0.01	0.81 (0.038)	<0.01	0.81 (0.04)	<0.01
I/S covariance	0.12 (0.05)	0.02	0.02 (0.055)	0.67	0.03 (0.06)	0.62
Residential Distance to Roadway						
→ I_{global}	0.06 (0.01)	<0.01	-0.01 (0.01)	0.35	-0.01 (0.01)	0.44
→ S_{global}	0.001 (0.03)	0.98	-0.001 (0.03)	0.98	-0.002 (0.03)	0.94
Covariates						
Age → I_{global}			-0.28 (0.01)	<0.01	-0.28 (0.01)	<0.01
Age → S_{global}			-0.41 (0.04)	<0.01	-0.41 (0.04)	<0.01
Education → I_{global}			0.35 (0.02)	<0.01	0.34 (0.02)	<0.01
Education → S_{global}			0.07 (0.04)	0.05	0.07 (0.04)	0.06
Male → I_{global}			-0.06 (0.01)	<0.01	-0.06 (0.01)	<0.01
Male → S_{global}			0.02 (0.03)	0.43	0.02 (0.03)	0.42
Black Non-Hispanic → I_{global}			-0.23 (0.02)	<0.01	-0.16 (0.02)	<0.01
Black Non-Hispanic → S_{global}			0.003 (0.03)	0.93	-0.01 (0.04)	0.90
Hispanic → I_{global}			-0.35 (0.02)	<0.01	-0.27 (0.02)	<0.01
Hispanic → S_{global}			0.05 (0.04)	0.23	0.04 (0.05)	0.39
Other Race → I_{global}			-0.07 (0.01)	<0.01	-0.06 (0.01)	<0.01
Other Race → S_{global}			0.06 (0.02)	<0.01	0.06 (0.02)	<0.01
Z-SES score → I_{global}					0.13 (0.01)	<0.01
Z-SES score → S_{global}					-0.01 (0.04)	0.76
Parameters	15		27		29	
TLI	0.990		0.992		0.992	
CFI	0.992		0.994		0.994	
SRMR	0.044		0.025		0.023	
RMESA (90% CI)	0.022 (0.017, 0.028)		0.015 (0.011,0.019)		0.014 (0.011,0.018)	

Model 1: crude model
Model 2: Adjusted for individual sociodemographic variables (age, education, sex, race/ethnicity)
Model 3: Adjusted for individual and neighborhood sociodemographic variables (Model 2 + Census based SES z-score)

Table A.9 Parameter Estimates of Conditioned Latent Growth Curve Models for the Association between $PM_{2.5}$ and Decline in Memory Domain						
	Model 1		**Model 2**		**Model 3**	
	Estimate (SE)	p-value	Estimate (SE)	p-value	Estimate (SE)	p-value
I_{mem} mean	0.82 (0.08)	<0.01	2.43 (0.08)	<0.01	4.49 (0.14)	<0.01
S_{mem} mean	-0.40 (0.24)	0.10	0.41 (0.05)	<0.01	3.92 (0.52)	<0.01
I_{mem} variance	0.98 (0.01)	<0.01	0.18 (0.01)	<0.01	0.62 (0.01)	<0.01
S_{mem} variance	0.99 (0.01)	<0.01	0.01 (0.002)	<0.01	0.78 (0.04)	<0.01
I/S covariance	0.20 (0.06)	<0.01	0.01 (0.002)	0.03	0.13 (0.07)	0.06
$PM_{2.5}$						
→ I_{mem}	-0.15 (0.01)	<0.01	-0.13 (0.01)	<0.01	-0.11 (0.01)	<0.01
→ S_{mem}	-0.08 (0.04)	0.06	-0.06 (0.04)	0.17	-0.05 (0.04)	0.19
Covariates						
Age → I_{mem}			-0.03 (0.01)	<0.01	-0.38 (0.02)	<0.01
Age → S_{mem}			-0.44 (0.05)	<0.01	-0.44 (0.05)	<0.01
Education → I_{mem}			0.29 (0.02)	<0.01	0.28 (0.02)	<0.01
Education → S_{mem}			0.05 (0.04)	0.20	0.04 (0.04)	0.26
Male → I_{mem}			-0.14 (0.01)	<0.01	-0.14 (0.01)	<0.01
Male → S_{mem}			0.03 (0.03)	0.30	0.03 (0.03)	0.29
Black Non-Hispanic → I_{mem}			-0.22 (0.02)	<0.01	-0.18 (0.02)	<0.01
Black Non-Hispanic → S_{mem}			-0.02 (0.03)	0.52	-0.01 (0.04)	0.70
Hispanic → I_{mem}			-0.34 (0.02)	<0.01	-0.29 (0.02)	<0.01
Hispanic → S_{mem}			0.04 (0.04)	0.36	0.05 (0.05)	0.31
Other Race → I_{mem}			-0.05 (0.02)	<0.01	-0.04 (0.05)	<0.01
Other Race → S_{mem}			0.003 (0.03)	0.92	0.004 (0.03)	0.88
Z-SES score→ I_{mem}					0.08 (0.02)	<0.01
Z-SES score→ S_{mem}					0.02 (0.03)	0.55
Parameters	15		27		29	
TLI	0.980		0.977		0.978	
CFI	0.983		0.983		0.984	
SRMR	0.042		0.025		0.024	
RMESA (90% CI)	0.032 (0.027,0.037)		0.025 (0.022, 0.029)		0.024 (0.021, 0.028)	

Model 1: crude model
Model 2: Adjusted for individual sociodemographic variables (age, education, sex, race/ethnicity)
Model 3: Adjusted for individual and neighborhood sociodemographic variables (Model 2 + Census based SES z-score)

Table A.10 Parameter Estimates of Conditioned Latent Growth Curve Models for the Association between PM_{10} and Decline in Memory Domain						
	Model 1		**Model 2**		**Model 3**	
	Estimate (SE)	p-value	Estimate (SE)	p-value	Estimate (SE)	p-value
I_{mem} mean	0.31 (0.05)	<0.01	4.08 (0.14)	<0.01	4.03 (0.14)	<0.01
S_{mem} mean	-0.90 (0.13)	<0.01	3.34 (0.45)	<0.01	3.38 (0.46)	<0.01
I_{mem} variance	0.99 (0.003)	<0.01	0.63 (0.01)	<0.01	0.63 (0.01)	<0.01
S_{mem} variance	1.00 (0.001)	<0.01	0.79 (0.04)	<0.01	0.79 (0.04)	<0.01
I/S covariance	0.20 (0.06)	<0.01	0.12 (0.07)	0.07	0.13 (0.07)	0.07
PM_{10}						
→ I_{mem}	-0.11 (0.01)	<0.01	-0.06 (0.01)	<0.01	-0.05 (0.01)	<0.01
→ S_{mem}	0.02 (0.03)	0.56	0.08 (0.03)	0.02	0.08 (0.03)	0.02
Covariate						
Age → I_{mem}			-0.38 (0.01)	<0.01	-0.38 (0.01)	<0.01
Age → S_{mem}			-0.45 (0.05)	<0.01	-0.45 (0.04)	<0.01
Education → I_{mem}			0.28 (0.02)	<0.01	0.27 (0.02)	<0.01
Education →			0.06 (0.04)	0.09	0.05 (0.04)	0.14
Male → I_{mem}			-0.14 (0.01)	<0.01	-0.14 (0.02)	<0.01
Male → S_{mem}			-0.03 (0.03)	0.29	0.03 (0.02)	0.27
Black Non-Hispanic → I_{mem}			-0.23 (0.02)	<0.01	-0.18 (0.08)	<0.01
Black Non-Hispanic → S_{mem}			-0.03 (0.03)	0.39	-0.02 (0.04)	0.64
Hispanic → I_{mem}			-0.35 (0.02)	<0.01	-0.29 (0.02)	<0.01
Hispanic → S_{mem}			0.05 (0.04)	0.23	0.06 (0.04)	0.18
Other Race → I_{mem}			-0.05 (0.01)	<0.001	-0.04 (0.01)	<0.01
Other Race → S_{mem}			0.01 (0.03)	0.845	0.01 (0.03)	0.79
Z-SES score→ I_{mem}					0.10 (0.02)	<0.01
Z-SES score→ S_{mem}					0.03 (0.03)	0.40
Parameters	15		27		29	
TLI	0.980		0.978		0.978	
CFI	0.983		0.984		0.984	
SRMR	0.045		0.027		0.026	
RMESA (90% CI)	0.031 (0.026, 0.037)		0.025 (0.022, 0.029)		0.024 (0.021, 0.027)	

Model 1: crude model
Model 2: Adjusted for individual sociodemographic variables (age, education, sex, race/ethnicity)
Model 3: Adjusted for individual and neighborhood sociodemographic variables (Model 2 + Census based SES z-score)

Table A.11 Parameter Estimates of Conditioned Latent Growth Curve Models for the Association between NO_2 and Decline in Memory Domain						
	Model 1		**Model 2**		**Model 3**	
	Estimate (SE)	p-value	Estimate (SE)	p-value	Estimate (SE)	p-value
I_{mem} mean	0.84 (0.07)	<0.01	4.35 (0.14)	<0.01	4.27 (0.14)	<0.01
S_{mem} mean	-0.69 (0.19)	<0.01	3.48 (0.48)	<0.01	3.48 (0.49)	<0.01
I_{mem} variance	0.97 (0.01)	<0.01	0.63 (0.01)	<0.01	0.62 (0.01)	<0.01
S_{mem} variance	0.99 (0.002)	<0.01	0.79 (0.04)	<0.01	0.79 (0.04)	<0.01
I/S covariance	0.20 (0.06)	<0.01	0.13 (0.07)	0.06	0.13 (0.07)	0.06
NO_2						
→ I_{mem}	-0.17 (0.01)	<0.01	-0.11 (0.01)	<0.01	-0.88 (0.01)	<0.01
→ S_{mem}	-0.03 (0.04)	0.42	0.02 (0.04)	<0.01	0.03 (0.04)	0.47
Covariates						
Age → I_{mem}			-0.37 (0.02)	<0.01	-0.37 (0.01)	<0.01
Age → S_{mem}			-0.44 (0.05)	<0.01	-0.45 (0.05)	<0.01
Education → I_{mem}			0.28 (0.02)	<0.01	0.27 (0.02)	<0.01
Education →			0.05 (0.04)	0.16	0.05 (0.04)	0.21
Male → I_{mem}			-0.14 (0.01)	<0.01	-0.14 (0.01)	<0.01
Male → S_{mem}			0.03 (0.03)	0.30	0.03 (0.03)	0.28
Black Non-Hispanic → I_{mem}			-0.22 (0.02)	<0.01	-0.18 (0.02)	<0.01
Black Non-Hispanic → S_{mem}			-0.027 (0.034)	0.417	-0.02 (0.04)	0.69
Hispanic → I_{mem}			-0.34 (0.02)	<0.01	-0.29 (0.02)	<0.01
Hispanic → S_{mem}			0.04 (0.04)	0.34	0.05 (0.05)	0.24
Other Race → I_{mem}			-0.05 (0.01)	<0.01	-0.04 (0.01)	<0.01
Other Race → S_{mem}			0.003 (0.03)	0.92	0.01 (0.03)	0.86
Z-SES score→ I_{mem}					0.08 (0.02)	<0.01
Z-SES score→ S_{mem}					0.03 (0.03)	0.35
Parameters	15		27		29	
TLI	0.981		0.978		0.979	
CFI	0.984		0.984		0.984	
SRMR	0.044		0.026		0.025	
RMESA (90%)	0.031 (0.026, 0.036)		0.025 (0.021, 0.028)		0.024 (0.02, 0.03)	
Model 1: crude model Model 2: Adjusted for individual sociodemographic variables (age, education, sex, race/ethnicity) Model 3: Adjusted for individual and neighborhood sociodemographic variables (Model 2 + Census based SES z-score)						

Table A.12 Parameter Estimates of Conditioned Latent Growth Curve Models for the Association between Residential Distance to Roadways and Decline in Memory Domain						
	Model 1		**Model 2**		**Model 3**	
	Estimate (SE)	p-value	Estimate (SE)	p-value	Estimate (SE)	p-value
I_{mem} mean	-0.03 (0.02)	0.04	4.00 (0.19)	<0.01	3.98 (0.14)	<0.01
S_{mem} mean	-0.86 (0.08)	<0.01	3.52 (0.45)	<0.01	3.56 (0.46)	<0.01
I_{mem} variance	0.99 (0.001)	<0.01	0.64 (0.01)	<0.01	0.63 (0.01)	<0.01
S_{mem} variance	1.00 (0.001)	<0.01	0.79 (0.04)	<0.01	0.79 (0.04)	<0.01
I/S covariance	0.20 (0.06)	<0.01	0.13 (0.07)	0.07	0.13 (0.07)	0.06
Residential Distance to Roadway						
→ I_{mem}	0.05 (0.01)	0.90	0.002 (0.01)	0.85	0.004 (0.01)	0.74
→ S_{mem}	-0.02 (0.03)	0.53	-0.02 (0.03)	0.45	-0.02 (0.03)	0.40
Covariates						
Age → I_{mem}			-0.39 (0.01)	<0.01	-0.39 (0.01)	<0.01
Age → S_{mem}			-0.44 (0.05)	<0.01	-0.44 (0.05)	<0.01
Education → I_{mem}			0.28 (0.02)	<0.01	0.27 (0.02)	<0.01
Education →			0.056 (0.03)	0.13	0.05 (0.04)	0.18
Male → I_{mem}			-0.14 (0.01)	<0.01	-0.14 (0.01)	<0.01
Male → S_{mem}			0.03 (0.03)	0.30	0.03 (0.03)	0.28
Black Non-Hispanic → I_{mem}			-0.23 (0.02)	<0.01	-0.18 (0.01)	<0.01
Black Non-Hispanic → S_{mem}			-0.03 (0.03)	0.39	-0.02 (0.04)	0.60
Hispanic → I_{mem}			-0.35 (0.02)	<0.01	-0.28 (0.02)	<0.01
Hispanic → S_{mem}			0.04 (0.04)	0.33	0.05 (0.05)	0.28
Other Race → I_{mem}			-0.05 (0.01)	<0.01	-0.04 (0.01)	<0.01
Other Race → S_{mem}			0.002 (0.03)	0.95	0.004 (0.03)	0.90
Z-SES score→ I_{mem}					0.10 (0.02)	<0.01
Z-SES score→ S_{mem}					0.03 (0.03)	0.44
Parameters	15		27		29	
TLI	0.981		0.978		0.978	
CFI	0.983		0.984		0.984	
SRMR	0.044		0.026		0.025	
RMESA (90% CI)	0.031 (0.026, 0.037)		0.025 (0.022, 0.028)		0.024 (0.021, 0.027)	

Model 1: crude model
Model 2: Adjusted for individual sociodemographic variables (age, education, sex, race/ethnicity)
Model 3: Adjusted for individual and neighborhood sociodemographic variables (Model 2 + Census based SES z-score)

Table A.14 Parameter Estimates of Conditioned Latent Growth Curve Models for the Association between $PM_{2.5}$ and Decline in Executive Function Domain						
	Model 1		**Model 2**		**Model 3**	
	Estimate (SE)	p-value	Estimate (SE)	p-value	Estimate (SE)	p-value
I_{exec} mean	1.31 (0.08)	<0.01	3.17 (0.15)	<0.01	3.04 (0.15)	<0.01
S_{exec} mean	-1.54 (0.73)	0.04	-0.39 (0.95)	0.68	-0.13 (0.93)	0.89
I_{exec} variance	0.94 (0.01)	<0.01	0.49 (0.02)	<0.01	0.49 (0.02)	<0.01
S_{exec} variance	0.93 (0.07)	<0.01	0.76 (0.18)	<0.01	0.74 (0.19)	<0.01
I/S covariance	0.22 (0.18)	0.22	0.18 (0.23)	0.42	0.19 (0.23)	0.41
PM2.5						
→ I_{exec}	-0.24 (0.01)	<0.01	-0.25 (0.01)	<0.01	-0.23 (0.01)	<0.01
→ S_{exec}	0.27 (0.13)	0.04	0.38 (0.16)	0.02	0.34 (0.14)	0.02
Covariates						
Age → I_{exec}			-0.22 (0.01)	<0.01	-0.22 (0.01)	<0.01
Age → S_{exec}			-0.21 (0.11)	0.04	-0.22 (0.10)	<0.01
Education → I_{exec}			0.45 (0.02)	<0.01	0.44 (0.02)	<0.01
Education → S_{exec}			0.21 (0.10)	0.04	0.23 (0.11)	0.03
Male → I_{exec}			0.05 (0.01)	<0.01	0.05 (0.01)	<0.01
Male → S_{exec}			-0.07 (0.06)	0.26	-0.07 (0.06)	0.24
Black Non-Hispanic → I_{exec}			-0.21 (0.02)	<0.01	-0.15 (0.02)	<0.01
Black Non-Hispanic → S_{exec}			-0.01 (0.06)	0.91	-0.10 (0.08)	0.20
Hispanic → I_{exec}			-0.35 (0.02)	<0.01	-0.28 (0.02)	<0.01
Hispanic → S_{exec}			0.11 (0.10)	0.24	0.002 (0.09)	0.98
Other Race → I_{exec}			-0.08 (0.01)	<0.01	-0.06 (0.01)	<0.01
Other Race → S_{exec}			0.11 (0.06)	0.05	0.09 (0.05)	0.07
Z-SES score→ I_{exec}					0.11 (0.02)	<0.01
Z-SES score→ S_{exec}					-0.19 (0.10)	0.05
Parameters	15		27		29	
TLI	0.986		0.986		0.986	
CFI	0.984		0.990		0.990	
SRMR	0.032		0.022		0.021	
RMESA (90% CI)	0.024 (0.019, 0.029)		0.018 (0.014, 0.021)		0.017 (0.014, 0.021)	

Model 1: crude model
Model 2: Adjusted for individual sociodemographic variables (age, education, sex, race/ethnicity)
Model 3: Adjusted for individual and neighborhood sociodemographic variables (Model 2 + Census based SES z-score)

Table A.15 Parameter Estimates of Conditioned Latent Growth Curve Models for the Association between PM_{10} and Decline in Executive Function Domain						
	Model 1		**Model 2**		**Model 3**	
	Estimate (SE)	p-value	Estimate (SE)	p-value	Estimate (SE)	p-value
I_{exec} mean	0.48 (0.05)	<0.01	2.25 (0.15)	<0.01	2.19 (0.15)	<0.01
S_{exec} mean	0.13 (0.25)	0.61	1.28 (0.89)	0.15	1.37 (0.89)	0.12
I_{exec} variance	0.97 (0.01)	<0.01	0.53 (0.02)	<0.01	0.51 (0.02)	<0.01
S_{exec} variance	0.99 (0.01)	<0.01	0.91 (0.07)	<0.01	0.87 (0.09)	<0.01
I/S covariance	0.14 (0.14)	0.31	0.05 (0.15)	0.74	0.07 (0.16)	0.65
PM_{10}						
→ I_{exec}	-0.18 (0.02)	<0.01	-0.19 (0.01)	<0.01	-0.17 (0.01)	<0.01
→ S_{exec}	-0.05 (0.07)	0.49	0.09 (0.07)	0.24	0.07 (0.07)	0.32
Covariates						
Age → I_{exec}			-0.21 (0.01)	<0.01	-0.21 (0.01)	<0.01
Age → S_{exec}			-0.20 (0.09)	0.03	-0.21 (0.01)	0.03
Education → I_{exec}			0.43 (0.02)	<0.01	0.42 (0.02)	<0.01
Education → S_{exec}			0.21 (0.10)	0.03	0.23 (0.10)	0.02
Male → I_{exec}			0.05 (0.01)	<0.01	0.05 (0.01)	<0.01
Male → S_{exec}			-0.06 (0.06)	0.28	-0.07 (0.06)	0.25
Black Non-Hispanic → I_{exec}			-0.22 (0.02)	<0.01	-0.15 (0.02)	<0.01
Black Non-Hispanic → S_{exec}			0.02 (0.06)	0.75	-0.10 (0.08)	0.19
Hispanic → I_{exec}			-0.38 (0.02)	<0.01	-0.29 (0.02)	<0.01
Hispanic → S_{exec}			0.14 (0.09)	0.14	0.002 (0.09)	0.99
Other Race → I_{exec}			-0.08 (0.01)	<0.01	-0.07 (0.01)	<0.01
Other Race → S_{exec}			0.11 (0.05)	0.04	0.09 (0.05)	0.06
Z-SES score→ I_{exec}					0.14 (0.01)	<0.01
Z-SES score→ S_{exec}					-0.23 (0.10)	0.02
Parameters	15		27		29	
TLI	0.991		0.992		0.992	
CFI	0.992		0.994		0.994	
SRMR	0.027		0.021		0.020	
RMESA (90% CI)	0.018 (0.012, 0.023)		0.013 (0.010, 0.017)		0.013 (0.009, 0.017)	

Model 1: crude model
Model 2: Adjusted for individual sociodemographic variables (age, education, sex, race/ethnicity)
Model 3: Adjusted for individual and neighborhood sociodemographic variables (Model 2 + Census based SES z-score)

Table A.16 Parameter Estimates of Conditioned Latent Growth Curve Models for the Association between NO_2 and Decline in Executive Function Domain						
	Model 1		**Model 2**		**Model 3**	
	Estimate (SE)	p-value	Estimate (SE)	p-value	Estimate (SE)	p-value
I_{exec} mean	1.33 (0.07)	<0.01	2.84 (0.15)	<0.01	2.73 (0.15)	<0.01
S_{exec} mean	-0.09 (0.40)	0.83	0.84 (0.88)	0.34	1.07 (0.91)	0.24
I_{exec} variance	0.92 (0.01)	<0.01	0.50 (0.02)	<0.01	0.49 (0.02)	<0.01
S_{exec} variance	0.99 (0.004)	<0.01	0.88 (0.09)	<0.01	0.85 (0.10)	<0.01
I/S covariance	0.16 (0.14)	0.26	0.10 (0.17)	0.56	0.11 (0.17)	0.53
NO_2						
→ I_{exec}	-0.29 (0.02)	<0.01	-0.25 (0.01)	<0.01	-0.23 (0.01)	<0.01
→ S_{exec}	0.05 (0.08)	0.74	0.19 (0.10)	0.05	0.13 (0.09)	0.14
Covariates						
Age → I_{exec}			-0.21 (0.01)	<0.01	-0.21 (0.01)	<0.01
Age → S_{exec}			-0.21 (0.10)	0.03	-0.21 (0.09)	0.02
Education → I_{exec}			0.43 (0.02)	<0.01	0.42 (0.02)	<0.01
Education → S_{exec}			0.21 (0.09)	0.03	0.23 (0.10)	0.02
Male → I_{exec}			0.05 (0.01)	<0.01	0.00 (0.01)	<0.01
Male → S_{exec}			-0.07 (0.06)	0.26	-0.07 (0.06)	0.23
Black Non-Hispanic → I_{exec}			-0.20 (0.02)	<0.01	-0.15 (0.02)	<0.01
Black Non-Hispanic → S_{exec}			-0.01 (0.06)	0.91	-0.10 (0.08)	0.18
Hispanic → I_{exec}			-0.35 (0.02)	<0.01	-0.29 (0.02)	<0.01
Hispanic → S_{exec}			0.11 (0.09)	0.23	-0.002(0.09)	0.98
Other Race → I_{exec}			-0.08 (0.01)	<0.01	-0.07 (0.01)	<0.01
Other Race → S_{exec}			0.11 (0.05)	0.04	0.09 (0.06)	0.23
Z-SES score→ I_{exec}					0.10 (0.02)	<0.01
Z-SES score→ S_{exec}					-0.20 (0.10)	0.03
Parameters	15		27		29	
TLI	0.988		0.989		0.989	
CFI	0.990		0.992		0.992	
SRMR	0.040		0.029		0.028	
RMESA (90%)	0.020 (0.015, 0.026)		0.016 (0.012, 0.019)		0.015 (0.011, 0.019)	

Model 1: crude model
Model 2: Adjusted for individual sociodemographic variables (age, education, sex, race/ethnicity)
Model 3: Adjusted for individual and neighborhood sociodemographic variables (Model 2 + Census based SES z-score)

Table A.17 Parameter Estimates of Conditioned Latent Growth Curve Models for the Association between Residential Distance to Roadway and Decline in Executive Function						
	Model 1		**Model 2**		**Model 3**	
	Estimate (SE)	p-value	Estimate (SE)	p-value	Estimate (SE)	p-value
I_{exec} mean	-0.10 (0.02)	<0.01	2.01 (0.15)	<0.01	1.95 (0.15)	<0.01
S_{exec} mean	-0.18 (0.13)	0.17	1.06 (0.83)	0.20	1.15 (0.82)	0.16
I_{exec} variance	0.99 (0.002)	<0.01	0.56 (0.02)	<0.01	0.54 (0.02)	<0.01
S_{exec} variance	0.99 (0.01)	<0.01	0.91 (0.07)	<0.01	0.86 (0.09)	<0.01
I/S covariance	0.11 (0.12)	0.39	0.02 (0.14)	0.91	0.04 (0.14)	0.79
Residential Distance to Roadway						
→ I_{exec}	0.07 (0.02)	<0.01	-0.01 (0.01)	0.57	-0.01 (0.01)	0.68
→ S_{exec}	0.09 (0.06)	<0.01	0.07 (0.06)	0.27	0.07 (0.06)	0.26
Covariates						
Age → I_{exec}			-0.24 (0.01)	<0.01	-0.23 (0.01)	<0.01
Age → S_{exec}			-0.18 (0.09)	0.04	-0.19 (0.09)	0.03
Education → I_{exec}			0.43 (0.02)	<0.01	0.42 (0.02)	<0.01
Education → S_{exec}			0.22 (0.10)	0.021	0.25 (0.10)	0.01
Male → I_{exec}			0.05 (0.01)	<0.01	0.05 (0.01)	<0.01
Male → S_{exec}			-0.06 (0.06)	0.27	-0.07 (0.10)	0.01
Black Non-Hispanic → I_{exec}			-0.23 (0.02)	<0.01	-0.14 (0.02)	<0.01
Black Non-Hispanic → S_{exec}			0.04 (0.06)	0.55	-0.09 (0.07)	0.22
Hispanic → I_{exec}			-0.37 (0.02)	<0.01	-0.27 (0.02)	<0.01
Hispanic → S_{exec}			0.16 (0.09)	0.10	0.01 (0.09)	0.95
Other Race → I_{exec}			-0.08 (0.01)	<0.01	-0.06 (0.01)	<0.01
Other Race → S_{exec}			0.11 (0.05)	0.036	0.08 (0.05)	0.07
Z-SES score→ I_{exec}					0.17 (0.02)	<0.01
Z-SES score→ S_{exec}					-0.25 (0.10)	0.01
Parameters	15		27		29	
TLI	0.992		0.993		0.992	
CFI	0.993		0.995		0.994	
SRMR	0.025		0.018		0.017	
RMESA (90% CI)	0.016 (0.011, 0.022)		0.013 (0.009, 0.017)		0.013 (0.009, 0.016)	

Model 1: crude model Model 2: Adjusted for individual sociodemographic variables (age, education, sex, race/ethnicity) Model 3: Adjusted for individual and neighborhood sociodemographic variables (Model 2 + Census based SES z-score)

Table A.18 Parameter Estimates of Conditioned Latent Growth Curve Models for the Association between $PM_{2.5}$ and Decline in Language Domain						
	Model 1		**Model 2**		**Model 3**	
	Estimate (SE)	p-value	Estimate (SE)	p-value	Estimate (SE)	p-value
I_{lang} mean	0.96 (0.08)	<0.01	3.36 (0.14)	<0.01	3.16 (0.14)	<0.01
S_{lang} mean	0.23 (0.29)	0.44	3.59 (0.63)	<0.01	3.67 (0.62)	<0.01
I_{lang} variance	0.97 (0.01)	<0.01	0.58 (0.01)	<0.01	0.56 (0.01)	<0.01
S_{lang} variance	0.99 (0.01)	<0.01	0.88 (0.04)	<0.01	0.87 (0.04)	<0.01
I/S covariance	0.03 (0.05)	0.52	-0.04 (0.06)	0.47	-0.03 (0.06)	0.55
PM2.5						
→ I_{lang}	-0.17 (0.01)	<0.01	-0.17 (0.01)	<0.01	-0.14 (0.01)	<0.01
→ S_{lang}	-0.08 (0.05)	0.10	-0.05 (0.05)	0.28	-0.07 (0.05)	0.18
Covariates						
Age → I_{lang}			-0.27 (0.01)	<0.01	-0.26 (0.01)	<0.01
Age → S_{lang}			-0.36 (0.05)	<0.01	-0.34 (0.05)	<0.01
Education → I_{lang}			0.39 (0.01)	<0.01	0.38 (0.01)	<0.01
Education → S_{lang}			-0.02 (0.04)	0.06	-0.02 (0.04)	0.67
Male → I_{lang}			0.01 (0.01)	0.29	0.01 (0.01)	0.23
Male → S_{lang}			-0.05 (0.04)	0.12	-0.07 (0.05)	0.14
Black Non-Hispanic → I_{lang}			-0.18 (0.02)	<0.01	-0.10 (0.02)	<0.01
Black Non-Hispanic → S_{lang}			-0.02 (0.04)	0.58	-0.06 (0.05)	0.22
Hispanic → I_{lang}			-0.35 (0.02)	<0.01	-0.25 (0.02)	<0.01
Hispanic → S_{lang}			0.03 (0.05)	0.59	-0.02 (0.06)	0.74
Other Race → I_{lang}			-0.05 (0.01)	<0.01	-0.03 (0.01)	0.02
Other Race → S_{lang}			0.03 (0.03)	0.42	0.02 (0.03)	0.56
Z-SES score→ I_{lang}					0.17 (0.01)	<0.01
Z-SES score→ S_{lang}					-0.07 (0.05)	0.15
Parameters	15		27		29	
TLI	0.992		0.996		0.996	
CFI	0.993		0.994		0.995	
SRMR	0.032		0.018		0.016	
RMESA (90%CI)	0.021 (0.015, 0.026)		0.013 (0.009, 0.017)		0.01 (0.008, 0.016)	

Model 1: crude model
Model 2: Adjusted for individual sociodemographic variables (age, education, sex, race/ethnicity)
Model 3: Adjusted for individual and neighborhood sociodemographic variables (Model 2 + Census based SES z-score)

Table A.19 Parameter Estimates of Conditioned Latent Growth Curve Models for the Association between PM_{10} and Decline in Language Domain						
	Model 1		Model 2		Model 3	
	Estimate (SE)	p-value	Estimate (SE)	p-value	Estimate (SE)	p-value
I_{lang} mean	0.55 (0.05)	<0.01	2.81 (0.13)	<0.01	2.72 (0.13)	<0.01
S_{lang} mean	-0.68 (0.16)	<0.01	2.75 (0.53)	<0.01	2.81 (0.53)	<0.01
I_{lang} variance	0.97 (0.01)	<0.01	0.57 (0.01)	<0.01	0.56 (0.01)	<0.01
S_{lang} variance	0.98 (0.01)	<0.01	0.86 (0.04)	<0.01	0.86 (0.04)	<0.01
I/S covariance	0.05 (0.05)	0.31	-0.03 (0.06)	0.56	-0.02 (0.06)	0.70
PM_{10}						
→ I_{lang}	-0.19 (0.01)	<0.01	-0.18 (0.01)	<0.01	-0.16 (0.01)	<0.01
→ S_{lang}	0.14 (0.04)	<0.01	0.19 (0.04)	<0.01	0.18 (0.04)	<0.01
Covariates						
Age → I_{lang}			-0.25 (0.01)	<0.01	-0.25 (0.01)	<0.01
Age → S_{lang}			-0.34 (0.04)	<0.01	-0.35 (0.05)	<0.01
Education → I_{lang}			0.38 (0.01)	<0.01	0.36 (0.01)	<0.01
Education → S_{lang}			0.01 (0.04)	0.91	0.01 (0.04)	0.88
Male → I_{lang}			0.01 (0.01)	0.47	0.01 (0.01)	0.36
Male → S_{lang}			-0.05 (0.03)	0.14	-0.05 (0.03)	0.14
Black Non-Hispanic → I_{lang}			-0.19 (0.02)	<0.01	-0.10 (0.02)	<0.01
Black Non-Hispanic → S_{lang}			-0.03 (0.04)	0.39	-0.07 (0.05)	0.17
Hispanic → I_{lang}			-0.37 (0.02)	<0.01	-0.26 (0.02)	<0.01
Hispanic → S_{lang}			0.05 (0.05)	0.35	0.004 (0.06)	0.99
Other Race → I_{lang}			-0.05 (0.01)	<0.01	-0.04 (0.01)	0.01
Other Race → S_{lang}			0.03 (0.03)	0.33	0.02 (0.03)	0.44
Z-SES score→ I_{lang}					0.18 (0.01)	<0.01
Z-SES score→ S_{lang}					-0.06 (0.05)	0.22
Parameters	15		27		29	
TLI	0.989		0.992		0.992	
CFI	0.991		0.994		0.994	
SRMR	0.034		0.018		0.017	
RMESA (90% CI)	0.023 (0.018, 0.029)		0.016 (0.012, 0.020)		0.015 (0.011, 0.019)	

Model 1: crude model
Model 2: Adjusted for individual sociodemographic variables (age, education, sex, race/ethnicity)
Model 3: Adjusted for individual and neighborhood sociodemographic variables (Model 2 + Census based SES z-score)

Table A.20 Parameter Estimates of Conditioned Latent Growth Curve Models for the Association between NO_2 and Decline in Language Domain						
	Model 1		**Model 2**		**Model 3**	
	Estimate (SE)	p-value	Estimate (SE)	p-value	Estimate (SE)	p-value
I_{lang} mean	1.19 (0.07)	<0.01	3.24 (0.13)	<0.01	3.07 (0.13)	<0.01
S_{lang} mean	-0.29 (0.23)	0.20	3.00 (0.57)	<0.01	3.08 (0.57)	<0.01
I_{lang} variance	0.94 (0.01)	<0.01	0.57 (0.01)	<0.01	0.55 (0.01)	<0.01
S_{lang} variance	1.00 (0.001)	<0.01	0.88 (0.03)	<0.01	0.88 (0.03)	<0.01
I/S covariance	0.04 (0.05)	0.50	-0.05 (0.06)	0.42	-0.04 (0.06)	0.50
NO_2						
→ I_{lang}	-0.25 (0.02)	<0.01	-0.20 (0.01)	<0.01	-0.16 (0.01)	<0.01
→ S_{lang}	0.14 (0.04)	0.76	0.06 (0.04)	0.19	0.04 (0.05)	0.32
Covariates						
Age → I_{lang}			-0.25 (0.01)	<0.01	-0.25 (0.01)	<0.01
Age → S_{lang}			-0.33 (0.05)	<0.01	-0.33 (0.05)	<0.01
Education → I_{lang}			0.38 (0.01)	<0.01	0.37 (0.01)	<0.01
Education → S_{lang}			-0.02 (0.04)	0.71	-0.01 (0.04)	0.75
Male → I_{lang}			0.01 (0.01)	0.37	0.01 (0.01)	0.30
Male → S_{lang}			-0.05 (0.03)	0.13	-0.05 (0.03)	0.13
Black Non-Hispanic → I_{lang}			-0.17 (0.02)	<0.01	-0.10 (0.02)	<0.01
Black Non-Hispanic → S_{lang}			-0.03 (0.04)	0.42	-0.06 (0.05)	0.20
Hispanic → I_{lang}			-0.34 (0.02)	<0.01	-0.25 (0.02)	<0.01
Hispanic → S_{lang}			0.03 (0.05)	0.61	-0.01 (0.06)	0.84
Other Race → I_{lang}			-0.05 (0.01)	<0.01	-0.04 (0.01)	0.01
Other Race → S_{lang}			0.02 (0.03)	0.43	0.02 (0.03)	0.55
Z-SES score→ I_{lang}					0.15 (0.02)	<0.01
Z-SES score→ S_{lang}					-0.06 (0.05)	0.26
Parameters	15		27		29	
TLI	0.991		0.994		0.994	
CFI	0.992		0.995		0.995	
SRMR	0.034		0.018		0.017	
RMESA (90%CI)	0.021 (0.016, 0.027)		0.014 (0.010, 0.018)		0.013 (0.010, 0.017)	

Model 1: crude model
Model 2: Adjusted for individual sociodemographic variables (age, education, sex, race/ethnicity)
Model 3: Adjusted for individual and neighborhood sociodemographic variables (Model 2 + Census based SES z-score)

Table A.21 Parameter Estimates of Conditioned Latent Growth Curve Models for the Association between Residential Distance to Roadway and Decline in Language Domain						
	Model 1		**Model 2**		**Model 3**	
	Estimate (SE)	p-value	Estimate (SE)	p-value	Estimate (SE)	p-value
I_{lang} mean	-0.03 (0.01)	0.08	2.56 (0.13)	<0.01	2.49 (0.13)	<0.01
S_{lang} mean	-0.31 (0.08)	<0.01	3.13 (0.54)	<0.01	3.18 (0.54)	<0.01
I_{lang} variance	0.99 (0.001)	<0.01	0.61 (0.01)	<0.01	0.58 (0.01)	<0.01
S_{lang} variance	0.99 (0.002)	<0.01	0.88 (0.03)	<0.01	0.88 (0.03)	<0.01
I/S covariance	0.03 (0.05)	0.57	-0.05 (0.06)	0.38	-0.04 (0.06)	0.49
Residential Distance to Roadway						
→ I_{lang}	0.03 (0.01)	0.03	-0.28 (0.01)	0.02	-0.03 (0.01)	<0.01
→ S_{lang}	0.03 (0.03)	0.38	0.03 (0.03)	0.34	0.03 (0.03)	0.37
Covariates						
Age → I_{lang}			-0.28 (0.01)	<0.01	-0.27 (0.01)	<0.01
Age → S_{lang}			-0.33 (0.04)	<0.01	-0.33 (0.05)	<0.01
Education → I_{lang}			0.38 (0.01)	<0.01	0.37 (0.01)	<0.01
Education → S_{lang}			-0.01 (0.04)	0.78	-0.01 (0.03)	0.37
Male → I_{lang}			0.01 (0.01)	0.40	0.01 (0.01)	0.30
Male → S_{lang}			-0.05 (0.03)	0.14	-0.05 (0.03)	0.13
Black Non-Hispanic → I_{lang}			-0.21 (0.02)	<0.01	-0.10 (0.02)	<0.01
Black Non-Hispanic → S_{lang}			-0.02 (0.04)	0.68	-0.06 (0.05)	0.25
Hispanic → I_{lang}			-0.36 (0.02)	<0.01	-0.24 (0.02)	<0.01
Hispanic → S_{lang}			0.04 (0.05)	0.40	-0.01 (0.06)	0.89
Other Race → I_{lang}			-0.05 (0.01)	<0.01	-0.03 (0.01)	0.03
Other Race → S_{lang}			0.03 (0.03)	0.41	0.02 (0.03)	0.56
Z-SES score→ I_{lang}					0.20 (0.01)	<0.01
Z-SES score→ S_{lang}					-0.07 (0.05)	0.15
Parameters	15		27		29	
TLI	0.992		0.994		0.9945	
CFI	0.993		0.996		0.996	
SRMR	0.029		0.015		0.014	
RMESA (90% CI)	0.020 (0.015, 0.026)		0.013 (0.009, 0.017)		0.012 (0.009, 0.016)	

Model 1: crude model
Model 2: Adjusted for individual sociodemographic variables (age, education, sex, race/ethnicity)
Model 3: Adjusted for individual and neighborhood sociodemographic variables (Model 2 + Census based SES z-score)

Table A.22 Sensitivity Analyses: Parameter Estimates of Conditioned Latent Growth Curve Models for the Association between Air Pollutants and Cognitive Decline , Individuals with > 2 NP Assessments (n=4,680)								
	$PM_{2.5}$		***PM_{10}***		***NO_2***		***Residential Distance to Roadway***	
	Estimate (SE)	p-value	Estimate (SE)	p-value	Estimate (SE)	p-value	Estimate (SE)	p-value
Global Cognitive Score								
→ I_{global}	-0.16 (0.01)	<0.01	-0.11 (0.02)	<0.01	-0.15 (0.02)	<0.01	0.001 (0.01)	0.92
→ S_{global}	-0.05 (0.04)	0.26	-0.07 (0.04)	0.04	-0.08 (0.04)	<0.01	-0.01 (0.03)	0.77
Memory Domain								
→ I_{mem}	-0.11 (0.01)	<0.01	-0.05 (0.01)	<0.01	-0.09 (0.01)	<0.01	0.01 (0.01)	0.66
→ S_{mem}	-0.05 (0.04)	0.25	0.07 (0.03)	0.03	0.03 (0.04)	0.40	-0.03 (0.03)	0.36
Executive Function Domain								
→ I_{exec}	-0.22 (0.01)	<0.01	-0.16 (0.02)	<0.01	-0.21 (0.02)	<0.01	0.002 (0.02)	0.98
→ S_{exec}	0.30 (0.02)	<0.01	0.04 (0.07)	0.60	0.09 (0.08)	0.27	0.05 (0.05)	0.37
Language Domain								
→ I_{lang}	-0.14 (0.01)	<0.01	-0.16 (0.01)	<0.01	-0.16 (0.01)	<0.01	-0.02 (0.01)	0.06
→ S_{lang}	-0.06 (0.05)	0.19	0.17 (0.04)	<0.01	0.04 (0.05)	0.33	0.02 (0.03)	0.52
All models fully adjusted for individual (age, education, sex, race/ethnicity) and neighborhood sociodemographic variables (Census based SES z-score)								

Table A.23. Sensitivity Analyses: Parameter Estimates of Conditioned Latent Growth Curve Models for the Association between Air Pollutants and Cognitive Decline, Individuals who survived 6 NP Visits (n=3,877)								
	$PM_{2.5}$		***PM_{10}***		***NO_2***		***Residential Distance to Roadway***	
	Estimate (SE)	p-value	Estimate (SE)	p-value	Estimate (SE)	p-value	Estimate (SE)	p-value
Global Cognitive Score								
→ I_{global}	-0.10 (0.02)	<0.01	-0.05 (0.02)	0.02	-0.09 (0.02)	<0.01	-0.01 (0.02)	0.61
→ S_{global}	0.05 (0.05)	0.32	-0.004 (0.04)	0.93	0.01 (0.04)	0.75	0.03 (0.03)	0.33
Memory Domain								
→ I_{mem}	-0.05 (0.02)	<0.01	-0.01 (0.02)	0.39	-0.04 (0.02)	0.07	-0.01 (0.02)	0.74
→ S_{mem}	0.03 (0.05)	0.54	0.12 (0.04)	0.003	0.10 (0.05)	0.02	0.03 (0.04)	0.47
Executive Function Domain								
→ I_{exec}	-0.20 (0.02)	<0.01	-0.14 (0.02)	<0.01	-0.19 (0.02)	<0.01	-0.003 (0.02)	0.88
→ S_{exec}	0.49 (0.18)	<0.01	0.16 (0.08)	0.16	0.24 (0.12)	0.04	0.07 (0.07)	0.34
Language Domain								
→ I_{lang}	-0.09 (0.01)	<0.01	-0.11 (0.01)	<0.01	-0.10 (0.01)	<0.01	-0.02 (0.01)	0.09
→ S_{lang}	-0.002 (0.06)	0.99	0.21 (0.05)	<0.01	0.08 (0.05)	0.16	0.004 (0.04)	0.92
All models fully adjusted for individual (age, education, sex, race/ethnicity) and neighborhood sociodemographic variables (Census based SES z-score)								

Table A.24 P-values for Cross-Product Terms to Assess Multiplicative Interaction in the Association of Air Pollution and Cognition			
	xSMOKE	**xAGECAT**	**xAPOE**
Global Cognitive Score			
$PM_{2.5}$			
→ I_{global}	<0.01	0.69	0.41
→ S_{global}	0.98	0.78	0.03
PM_{10}			
→ I_{global}	<0.01	0.02	0.97
→ S_{global}	0.31	0.49	0.10
NO_2			
→ I_{global}	<0.01	0.38	0.80
→ S_{global}	0.78	0.73	0.12
Residential Distance to Roadway			
→ I_{global}	<0.01	0.70	0.11
→ S_{global}	0.29	0.66	0.73
Memory Domain			
$PM_{2.5}$			
→ I_{mem}	0.01	<0.01	0.52
→ S_{mem}	0.59	0.954	0.10
PM_{10}			
→ I_{mem}	<0.01	<0.01	0.57
→ S_{mem}	0.50	0.90	0.15
NO_2			
→ I_{mem}	<0.01	<0.01	0.69
→ S_{mem}	0.82	0.35	0.05
Residential Distance to Roadway			
→ I_{mem}	<0.01	0.78	0.22
→ S_{mem}	0.12	0.98	0.77
Executive Function Domain			
$PM_{2.5}$			
→ I_{exec}	<0.01	0.43	0.79
→ S_{exec}	0.55	0.50	0.08
PM_{10}			
→ I_{exec}	<0.01	0.90	0.08
→ S_{exec}	0.41	0.06	0.78
NO_2			
→ I_{exec}	<0.01	0.72	0.52
→ S_{exec}	0.92	0.16	0.75
Residential Distance to Roadway			
→ I_{exec}	0.41	<0.01	0.07
→ S_{exec}	0.95	0.25	0.36
Language Domain			
$PM_{2.5}$			
→ I_{lang}	<0.01	<0.01	0.61

→ S_{lang}	0.56	0.58	0.52
PM_{10}			
→ I_{lang}	<0.01	<0.01	0.24
→ S_{lang}	0.38	0.67	0.24
NO_2			
→ I_{lang}	<0.01	<0.01	0.16
→ S_{lang}	0.44	0.48	0.74
Residential Distance to Roadway			
→ I_{lang}	0.12	0.75	0.11
→ S_{lang}	0.69	0.98	0.81
All models fully adjusted for individual (age, education, sex, race/ethnicity) and neighborhood sociodemographic variables (Census based SES z-score), and potential effect modifiers			

Figure A.1 Analytical Sample Size for the Combined NOMAS-WHICAP Cohort

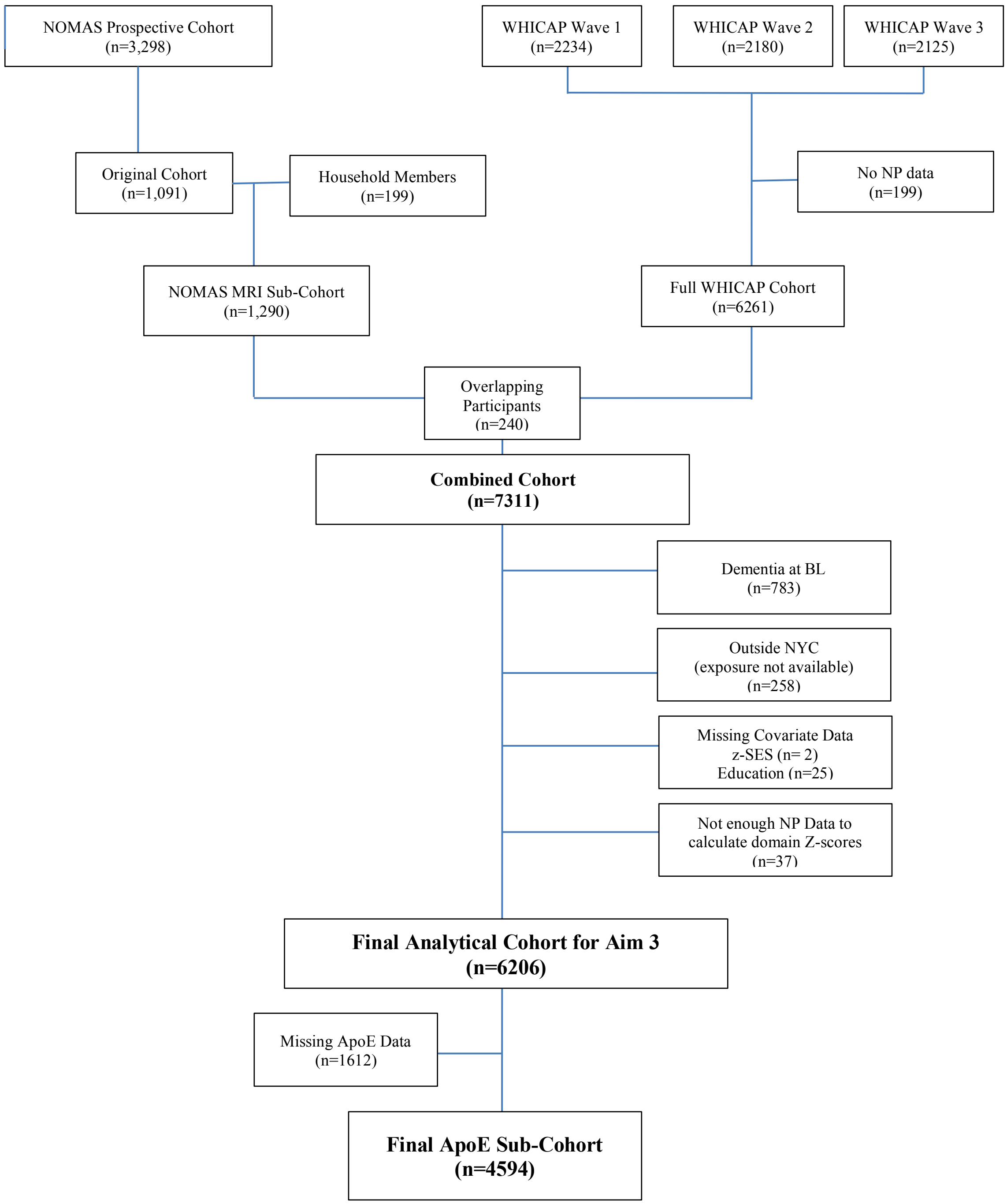

Figure A.2. Path diagram for the fully adjusted latent growth curve model for trajectories of global cognitive score.